Neurology

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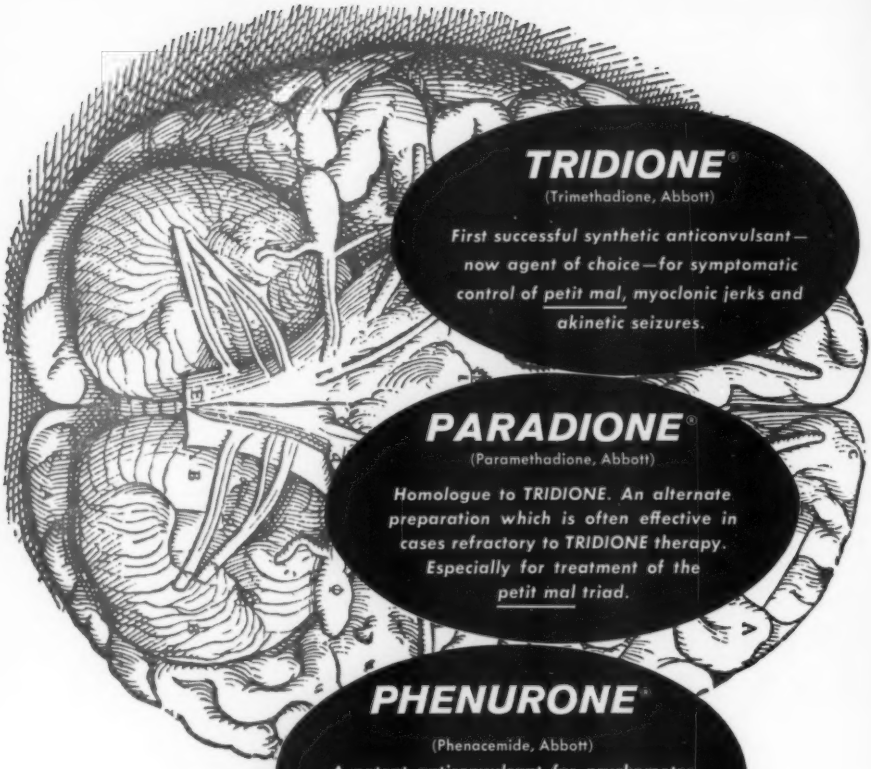

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INFORMATION FOR *Authors*

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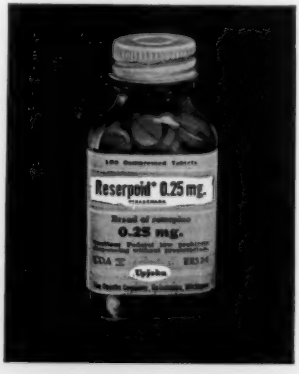

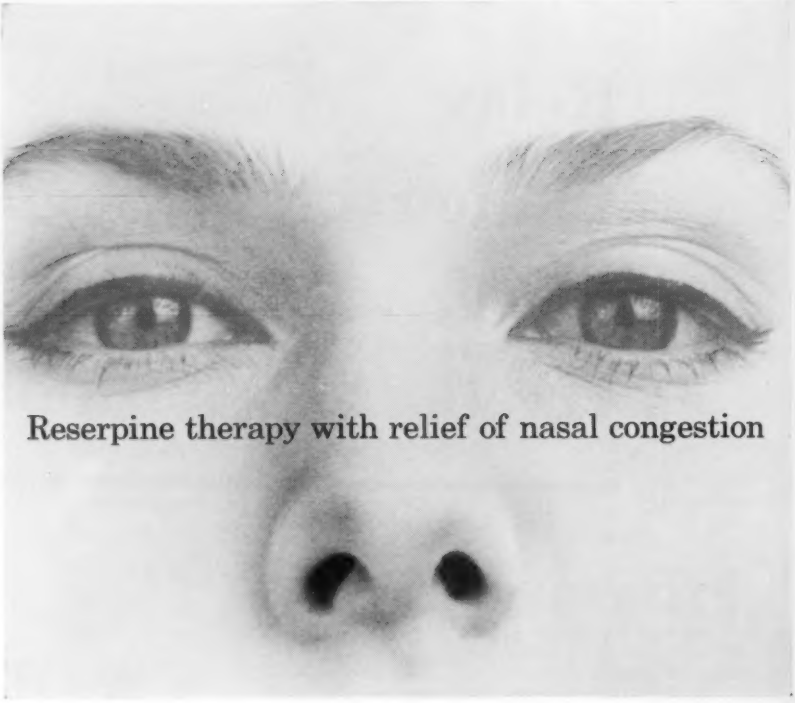

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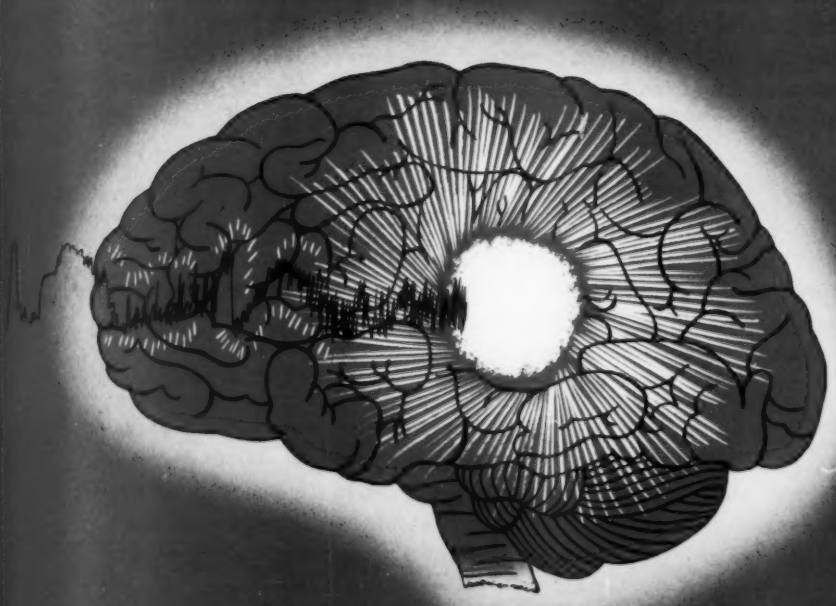

In epilepsy

NOTABLE RESULTS REPORTED WITH "MYSOLINE" IN 63 PER CENT OF PATIENTS REFRACTORY TO OTHER ANTICONVULSANTS.

The Doyle and Livingston report* covers 100 patients, mostly children, the majority ranging in age from 2 to 14 years. In 64 the epilepsy was of idiopathic origin, and in 36 it was due to organic causes. Other anticonvulsants in maximum dosages had proved ineffective in 81 of these patients for at least one year previously.

In 42 of the 81 patients who had been receiving other anticonvulsants, transition to "Mysoline" alone was completed in about 2 months; the other 39 were continued on combination therapy throughout the observation period (from 3 months to 1 year). The daily dose of "Mysoline" ranged from 0.375 Gm. to 1.5 Gm., depending on the age of the patient.

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*Doyle, P. J., and Livingston, S.: J. Pediat. 43:413 (Oct.) 1953.

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Editorial: Brit. M. J. *1*:1028 (May 1) 1954.

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Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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Grand Mal	613	175 (28.5%)	253 (41.2%)	185 (30.3%)
Psychomotor	130	10 (7.7%)	65 (50%)	55 (42.3%)

EPILEPTIC PATIENTS HAD RECEIVED NO OTHER MEDICATION

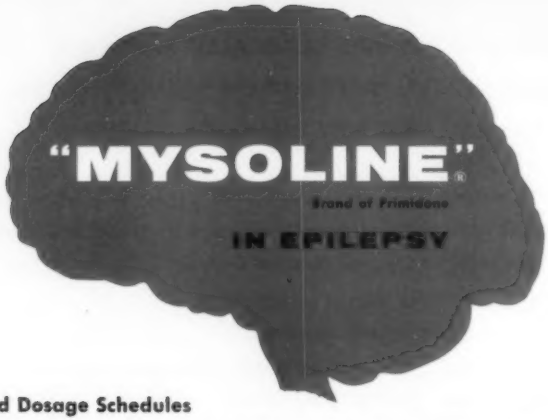
"Mysoline" alone was employed.

Type of Seizure	No. of Patients	Completely Controlled	50-90% Improved	Less than 50%
Grand Mal	214	172 (80%)	15 (7%)	27 (13%)
Psychomotor	29	19 (65%)		10 (35%)

†"Seizure discharge, the physiological basis of clinical epilepsy, is a process by which 'a portion of the cerebral nerve network (is converted) from a submaximally active asynchronous mosaic with an internal self-regulating inhibitory system to a maximally active hyperdischarging and hypersynchronized functional unit capable of detonating other regions of the brain with which it has connection'."

Kaufman, I. C., and Isenberg, S.: M. Clin. North America *36*:1381 (Sept.) 1952.

SEE NEXT PAGE FOR COMPLETE DOSAGE SCHEDULES



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When dosage is increased beyond 1 Gm., the daily intake is administered in four divided doses, and increments of 0.25 Gm. are added at weekly intervals as indicated above. Children 8 years and older are usually able to tolerate the same dosage as adults. ("Mysoline" is not recommended for use in dosages over 2 Gm. daily.)

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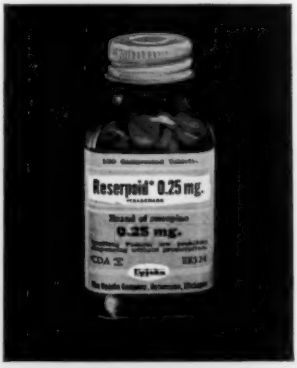

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*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.

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Kinross-Wright, V.: Postgrad. Med. 16:297 (Oct.) 1954.

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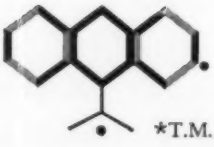

*T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of chlorpromazine.

Volume 5 Neurology *Number 11*

Neurologic Manifestations in Collagen Diseases

Problems of Prognosis and Treatment

Gilbert H. Glaser, M.D.

THE PRESENT essentially morphologic concept of the collagen diseases or disorders of connective tissue includes acute systemic lupus erythematosus, polymyositis or dermatomyositis, periarteritis nodosa, scleroderma, rheumatoid arthritis, and rheumatic fever.[29,43] Whether these diseases are intimately related with regard to causative factors and really should be grouped together is still a matter of some controversy.[29,30,43] However, increasing interest in these conditions has led to developing awareness of the occurrence and significance of neurologic manifestations. The evidence of neurologic involvement derives from the occurrence of a myriad of signs and symptoms[4,8,10,19,25,28,31,32,33,36,48,58] such as focal and generalized convulsions, aphasia, muscle weakness, cranial and peripheral nerve defects, electroencephalographic changes, organic mental deficits clinically or only on psychological testing, and abnormalities of the cerebrospinal fluid protein. Diffuse and focal lesions of the central and peripheral nervous systems occur in these diseases especially in relation to involvement of smaller blood vessels.[10,19,30,31,35] Yet, there is often a lack of clinical and pathologic correlation in that extensive lesions may exist without neurologic signs or symptoms.[19,31] The extent of this problem is shown by the recent report of an over 80 per cent occurrence of abnormal findings involving the central nervous system in a series of 51 patients with disorders of collagen.[33] These abnormalities were determined, in addition to the clinical findings, by changes in psychometric tests, electroencephalograms, and cerebrospinal fluid.

This paper will be concerned primarily with the problems of prognosis

From the section of neurology, department of internal medicine, Yale University School of Medicine, New Haven, Connecticut.

Presented at the seventh annual meeting of the American Academy of Neurology, Houston, Texas, April 30, 1955.

and treatment in the disorders of systemic lupus erythematosus, polymyositis and dermatomyositis, periarteritis nodosa, and scleroderma since the neurologic picture may assume predominance during the natural history of each.

When these four diseases are considered diagnostically, it is realized that the protean manifestations and variable course often make it extremely difficult to distinguish between them. In order to focus on the similarities and differences, the general clinical characteristics of these conditions are presented in table 1. The involvements of the nervous system in all of these diseases are usually secondary to proliferative and degenerative changes in the connective tissue of the smaller blood vessels. These changes lead to occlusion or rupture of the blood vessel, with resultant disseminated ischemic changes in the central nervous system or peripheral nerves. The lesions of periarteritis and lupus differ in certain basic details, but it is considered that the vascular changes in scleroderma may be closely related to that of lupus, possibly representing a more chronic type of a similar process.[19, 30] The lesions in dermatomyositis and polymyositis more directly involve muscle tissue in degeneration.[14]

It is of great interest that there is an unexplained differential involvement of the divisions of the nervous system in these different conditions. For example, in systemic lupus erythematosus there are primarily disseminated focal lesions in the cerebral cortex, especially in the perisulcal regions of the gray matter,[19]

TABLE 1

COMPARATIVE CLINICAL FEATURES OF CERTAIN COLLAGEN DISEASES

(Based on references 4, 8, 10, 19, 25, 28, 31, 32, 33, 36, 48, 58)

Manifestations	*Systemic lupus erythematosus*	*Periarteritis nodosa*	*Dermatomyositis*	*Scleroderma*
Fever	++++	+++	+++	++
Weight loss	++++	+++	+++	++
Light sensitivity	+++	—	+	+
Arthritic	+++	++	+	+++
Cutaneous	++++	+++	++++	++++
Central nervous	+++	++	+	+
Peripheral nerve	+	+++	+	+
Muscular	++	++	++++	+
Raynaud's	++	++	++	+++
Renal	++	+++	—	—
Cardiac	+++	+++	+	+
Hypertensive	+	+++	—	—
Pulmonary	++	++	—	+
Abdominal	++	++++	—	—
Lymph node	+++	+	+	+
Retinal	+	+	+	+
Anemia	++++	+++	+	+
Leukocytes	Reduced	Increased	Normal	Normal
Eosinophilia	+	++	+	+
Leukocytes	+++	++	+	+
L.E. cells	++++	—	—	—

++++ = 75–100% +++ = 50–75% ++ = 25–50% + = Less than 25% — = Chance occurrence

and this localization probably accounts for the high incidence of convulsive seizures occurring in this disorder. There are reports, however, of a few cases of peripheral nerve involvement in systemic lupus. Although the vascular lesions in periarteritis nodosa involve the cerebrum, there is, in contrast to the situation in lupus, a much higher incidence of single or multiple peripheral nerve involvement. In dermatomyositis the lesions may involve muscle tissue primarily with only a minimal incidence of central nervous system damage. In scleroderma there is a high incidence of peripheral vascular lesions, with a possible sympathetic nervous component and the occurrence of Raynaud's phenomenon, and only rare central nervous system changes. A special form of periarteritis nodosa may be limited to the temporal artery (temporal arteritis), or this may be a predominant involvement in a more general picture of periarteritis. However, the late onset of this local lesion, occurring usually between the ages of 60 and 80, make it a somewhat more peculiar syndrome. Another unusual association of periarteritis nodosa is with interstitial keratitis and bilateral vestibular symptoms and deafness, or Cogan's syndrome.[37]

The concept of polymyositis has been broadened recently.[14] A predominantly symmetric proximal muscle weakness may occur not only in association with cutaneous lesions as in dermatomyositis, but also with scleroderma or acrosclerosis and rheumatoid arthritis. In addition there may be a polymyositis that exists alone without any other systemic involvement. The diagnosis is helped by muscle biopsy and electromyographic features of muscle degeneration. Some cases have the appearance of a muscular dystrophy of menopausal onset.[50]

Sex incidence varies a great deal between these different conditions. Systemic lupus erythematosus is four times more common in females, and periarteritis nodosa is four times more common in males. Scleroderma is more common in females and the sex incidence is about equal in dermatomyositis. There is a wide range of age incidence in these disorders, generally between ten and 50. However, very few cases of scleroderma occur before the age of 30.

In addition to actual central nervous system lesions related to the basic disease process, neurologic signs and symptoms may be the result of secondary disturbances due to azotemia, fever, hypertension, congestive failure, hemorrhagic tendencies, or the toxic effects of treatments. It has been indicated that involvement of the central nervous system, for example, by convulsions or a hemiplegia, is often a preterminal or terminal event and represents a poor prognostic sign.

PROGNOSIS AND THE NATURAL HISTORY OF COLLAGEN DISORDERS

All considerations of therapy must have as background a complete understanding of the natural history of the disease being treated. In all of these disorders of collagen the course and prognosis are regarded now to be extremely variable.[10, 14, 16, 25, 28, 32, 36, 48] For example, many cases of periarteritis nodosa (at least 50 per cent) have remissions, often of several years' duration. Yet, when death occurs it is usually within two years after the onset of symptoms, so that a duration over two years implies a better prognosis. The prognosis is graver when renal and central nervous system lesions exist. In sys-

temic lupus erythematosus the various case series analyses are not altogether in agreement, but there is evidence that at least 20 per cent of the patients survive more than five years.[28] Actually, in one series[25] there was an estimated 50 per cent survival rate four years after the diagnosis. In this group 78 per cent of the patients survived the first year. In scleroderma[32] the evidence is that one half of the patients are dead within five years, and that the surviving 50 per cent may have a very prolonged course lasting many years with associated debilitation and intercurrent infections. Again, in dermatomyositis[48] the course is extremely variable but apparently 50 to 60 per cent of the patients die, usually within two years. The remainder of the patients have spontaneous complete remissions or severe residuals with permanent atrophy, contractures, and weakness of muscles. In other cases periodic exacerbations may occur. All evaluations of therapy must consider these data which indicate that many patients with these collagen diseases may have a prolonged course with spontaneous remissions and exacerbations.

Because of the development of the highly accurate L.E. cell test,[24] there has been more study of the occurrence and course of systemic lupus erythematosus in recent years. The problems concerning prognosis and treatment of systemic lupus are basic to all of the collagen diseases. Certainly the incidence of the diagnosis of systemic lupus is increasing because of the L.E. test,[10] and it has been estimated that systemic lupus is at least one half as common as rheumatic fever and more common than pernicious anemia, Hodgkin's disease, and leukemia. It is now known that at least 40 per cent of cases have spontaneous remissions and these remissions have been multiple in 20 per cent. The clinical picture is now regarded to be much more pleomorphic than realized heretofore. In systemic lupus there may be a high incidence of lesions involving the central nervous system.[10,25,28,52] In about 2 per cent of patients convulsive seizures may be the first symptom, and during the course of the disease it has been estimated that up to 30 per cent of the patients may have seizures, 18 per cent may have other signs of chronic damage of the central or peripheral nervous system, and at least 30 per cent may have psychotic reactions secondary to brain damage. Neurologic disturbances usually develop during a very active phase of the disease or exacerbation, especially preterminally or terminally.

Remissions in systemic lupus may vary from several weeks to many years. Without treatment the remissions generally may be from one to four years, but occasionally remissions of over ten years have been reported. In a few cases these improvements may lead to full activity without discomfort for several years. Symptoms referable to the joints and skin and general bodily reactions such as fever are likely to remit. Less remissive are symptoms and signs involving the lungs, heart, and especially the kidney and nervous system. One or many organ systems may be involved during exacerbation. It is of great importance that secondary infections or severe drug reactions may produce trigger mechanisms enhancing the activity of the disease process with a more rapid progress or acute exacerbation. It should be mentioned that it is often very difficult to determine the onset and subsequent course of these disorders, since the history at onset may be very obscure and

only minor undiagnosed symptoms may exist for a long time. In certain cases there may only be a recurrent mild illness with long asymptomatic intervals. These factors must be taken into consideration when acute treatment and long-term management are planned and evaluated.

PRINCIPLES OF TREATMENT AND COMPLICATIONS OF TREATMENT, WITH SPECIAL REFERENCE TO NERVOUS SYSTEM MANIFESTATIONS

The problems and methods of treatment in all of these collagen diseases are similar. The principles and methods of treatment, therefore, will be discussed in nonspecific terms at first and then special reference will be made to the individual disorders. Since the actual cause of these diseases is unknown, curative treatments are not available. However, much in the way of suppressive therapy can often be accomplished.

The background of therapy in these diseases is so-called supportive treatment. Bedrest and limitation of activity are important during acute exacerbations. In polymyositis and scleroderma physical therapy may be necessary in order to prevent deforming contractures. The use of local applications to reduce discomfort from cutaneous lesions, the control of pain with suitable analgesics, transfusions for anemia, and digitalis and salt restriction for cardiac failure may be important adjuncts. All patients should be screened for complicating infections which may be contributing to a febrile state, and if these are present appropriate antibiotics should be administered.

During recent years the use of adrenal steroid hormone therapy, either by administering cortisone directly or corticotropin (ACTH), has become the cornerstone of therapy of these collagen diseases. These hormones produce multiple metabolic and other pharmacologic effects[59] which have to be correlated with the clinical responses. The effects do not result in a specific cure for the disorder, but suppression of the activity of the disease process may occur. Hormonal therapy represents the only major control measure available at present. The over-all survival of these patients may be lengthened, but adequate control data concerning this are not yet available. It is very difficult to evaluate the effects of treatment because of the protean nature of the clinical manifestations and the variable course with tendency toward spontaneous remissions, as described above. Actually, in none of these diseases is there an adequate index of the basic activity of the disease process. In systemic lupus the presence of L.E. cells is an excellent diagnostic aid, but these cells may persist long after the symptoms are relieved and this test cannot be used as an objective index of disease activity.[25]

More information has accumulated concerning the use of adrenal steroid therapy in systemic lupus than in any of the other collagen disorders. Therefore, the treatment of this condition will be outlined as a prototype. Many hundreds of patients with this disease have been so treated thus far, with follow-up studies of at least four years in numerous cases.[3,13,25,26,40,52,53]

The following dosage schedules of ACTH and cortisone have been varied somewhat by different investigators, but certain general rules have been developed. The most important is that the results of treatment are followed with regard to the clinical response of symptoms and signs rather than changes in

laboratory findings. The initial dose of ACTH has been 80 to 120 mg. intramuscularly daily in four divided doses, or the equivalent of 40 to 60 mg. of ACTH in gelatine in two doses, or 20 to 40 mg. intravenously in 5 per cent glucose in eight to 12 hours. Cortisone has been started initially in 200 to 400 mg. dosage per day orally in four to six divided doses. In addition, these patients, all hospitalized, are kept on a salt-limited diet; occasionally mercurial diuretics have been administered for edema and digitalis for cardiac failure. It is also important to administer potassium chloride, 3 to 6 gm. per day, except in patients with significant renal involvement, in order to counteract induced hypopotassemia. Daily weight and blood pressure measurements are taken. If after several days there is no response to this initial dosage, the dosage levels are raised until a favorable effect is obtained or significant signs of overdosage occur. All agree that there is no significant difference between the administration of ACTH and cortisone, and there has been no special preference by the different investigators. Once significant effects occur, the amount with which this improvement has developed is continued until the major symptoms are suppressed maximally. After this the hormones are reduced stepwise, for example, 10 to 20 mg. of ACTH daily or 25 to 50 mg. of cortisone every two to four days. If reduction in dosage produces recrudescence of symptoms, an increase is indicated and maintenance therapy considered. If reducing the hormones produces no significant changes, this should continue until no further hormone is administered. This method allows for a great deal of individual variation, and in one series[25] the duration of treatment of the individual acute phase in over 60 patients varied from two to 68 days. It is recommended that patients remain in the hospital during the immediate period after treatment because of a relatively high incidence (about 30 per cent) of a temporary relapse or rebound occurring in the first week, which usually subsides without treatment into a phase of remission. Certainly if an acute relapse or exacerbation occurs after a period of remission, hormonal therapy should be reinstituted. If there is no lasting remission after a single course of hormone therapy, maintenance treatment is recommended. There are many problems concerned with maintenance therapy, particularly those relating to the complications due to the long-term administration of these hormones which will be discussed below. The dosages used in average situations for maintenance therapy are cortisone, 50 to 100 mg. in divided doses per day, and ACTH, 25 to 75 mg. in divided doses per day. The use of the long-acting preparations of ACTH limit the number of injections required. There may be some value in alternating courses of ACTH and cortisone in order to prevent long-term adrenocortical suppression. An advantage of cortisone is the production of less salt retention. In addition, there is less of a risk of inducing an allergic reaction with cortisone, but this is quite rare with presently available preparations of ACTH.

There is still no uniformity of opinion concerning the utilization of these hormones in continued or intermittent fashion for long-term management. In one series[25] several patients, becoming asymptomatic during the course of hormone therapy, did not show any changes in remaining phenomena such as presence of L.E. cells and increased sedi-

mentation rate with continued hormonal therapy, and no relapse occurred after the hormones were discontinued. These workers felt that intermittent use of the hormones is to be preferred because of the risks associated with continued therapy. However, there is the other opinion[13] that continued therapy with ACTH or cortisone is necessary and that, even in acute treatment, the production of an obvious Cushing's state is important as the endpoint determining effectiveness of therapy. These differences cannot be answered as yet, particularly because of the difficulties of evaluation of therapy due to the variations in spontaneous course of the disease.

The actual effects of ACTH and cortisone on the specific manifestations of systemic lupus may be summarized as follows: Fever is usually diminished within one to five days and joint symptoms disappear within one week. Mucocutaneous and serosal lesions are relieved in one to four weeks, and Raynaud's phenomenon may be remarkably diminished in one to three weeks. The effects on renal, cardiac, pulmonary, and gastrointestinal signs and symptoms are extremely variable. In some cases improvements in these areas may be quite marked within three to four weeks, but in others little change occurs. There is no consistent effect on retinal cytoid bodies. Anemia is usually improved, but the effects on the leukocyte count are somewhat variable. Usually the L.E. cells persist during spontaneous and drug-induced remissions, but in a few cases they have been reported to be less numerous. Effects on serum proteins and the erythrocyte sedimentation rate have been quite variable, with only occasional changes toward normality reported. Hypertension often persists in association with unaltered renal disease. Abnormal mental states occurring in association with acute exacerbations of lupus lesions have shown a variable response, and similarly other neurologic involvements have not shown dramatic improvements. In one series[45] seizures were reported to have diminished, but in others[13,25,53] they persisted unchanged. Also, electroencephalographic abnormalities present before hormonal administration have shown no change, improvement, or worsening during the administration of ACTH and cortisone.[39,45] It is of great importance that it is often very difficult to evaluate effects on these nervous system manifestations because of the occurrence of similar manifestations as complications of hormonal therapy. For example, in certain series[13,25,52] the incidence of convulsions and abnormal mental reactions increased in patients receiving these hormones. This is particularly so in patients in severe acute exacerbation. These reactions in some instances may merely reflect a more severe illness rather than an actual effect due to the therapeutic agents.

Available information indicates that about two-thirds of patients with acute systemic lupus have an excellent initial response to hormonal therapy and that induced remissions may last without further therapy one to 42 months, with an average of six to 12 months. Occurrence of a remission did not appear to depend on the severity of the illness at the time of the treatment. In a small number of patients the disease may remain quiescent or mildly active for varying periods of time after a single course of therapy, but in others the disease progresses despite recurrent treatment, especially when renal and central nervous system lesions are present. The over-all

response during the past four or five years in most series seems to indicate that at least one-third of patients died despite therapy and two-thirds of patients remained alive with varying intensities of the disease process. In these the question of maintenance is still a problem. One-half appear to require maintenance therapy, and the remainder are minimally symptomatic or asymptomatic without therapy or have had no response. These results concerning survival in association with hormonal therapy appear to be somewhat better when compared with the natural spontaneous course of this disease. However, significant quantitative data are not yet available.

There have been many other drugs recommended for the treatment of systemic lupus, but only a few of these will be discussed here because of their importance. These drugs may be of some help in patients developing complications requiring the discontinuation of hormonal therapy. Even without the development of these complications, it might be advisable to utilize these substances alternating with steroid therapy in order to allow a period of reversal of the catabolic effects of long-term steroid therapy, such as the healing of osteoporosis and the reversal of a negative nitrogen balance. The patient, therefore, would be in a better condition for further steroid hormone therapy when indicated. Certainly, acetylsalicylic acid remains a useful adjunct.[25] This drug will reduce fever and cause the patient to feel generally better. In addition it may improve arthritic symptoms, but usually it has no other significant suppressive effects. Recently, quinacrine (Atabrine),[21] a drug used for chronic discoid lupus, has been administered to patients with acute lupus with variable results. The therapeutic effect of this drug is not related to its antimalarial property. The dosage of quinacrine has varied from 1 mg. per day in sensitive patients to 600 mg. per day initially. In most cases 300 mg. per day has been administered for one week and then the dose has been increased to a state of further clinical improvement or toxicity. Complications of gastroenteritis, dermatitis, aplastic anemia, and psychosis have led to the discontinuation of quinacrine. The response has been reported to be best in patients with a less active or subacute disease process.

It has been indicated above that the response of renal involvement is often minimal during hormonal therapy. Because of this it has been recommended that nitrogen mustard therapy be administered along with ACTH and cortisone.[11] This treatment is potentially hazardous, but in some patients with edema and a nephrotic nephropathy the results have been promising. Another substance that has been recommended is TEM (triethylene melamine), but this is regarded as a highly toxic and unpredictable agent.[11] Para-aminobenzoic acid has been recommended because of the light sensitivity of these patients. The results have been extremely variable and there is danger of severe side reactions.[25]

The general principles of and responses to therapy in the other collagen diseases are similar to those of systemic lupus. However, the accumulated experience has been much more limited, and in addition the reports show a less favorable over-all response. Steroid hormone therapy may induce remissions in periarteritis nodosa but with less frequency and completeness than in systemic lupus.[1,17,34,49,57] Also, relapses are

more apt to occur after cessation of therapy. However, because of the occurrence of spontaneous remission in periarteritis nodosa, it may be worthwhile to administer cortisone or ACTH in order to suppress an otherwise fatal reaction and provide protection until the disease process abates. Muscle biopsy has been advocated as a means of following the changes.[34,49] The response of peripheral neuropathy has not been very remarkable and it is often very difficult to control the pain associated with this condition. This pain may require the careful use of the various analgesic agents. It is important to realize, however, especially in periarteritis, that the healing of the vascular lesions may occur with a good deal of intimal proliferation, more so than in lupus, resulting in obliteration of the small blood vessel and further ischemia and infarction of the parenchymal tissues.[1] This is especially dangerous in patients with kidney and central nervous system lesions and may account for the persistence of significant or increased signs and symptoms in association with or following hormonal therapy. Recently the suggestion has been made that antihypertensive drugs and possibly sympathectomy be considered as adjuncts in the treatment of periarteritis nodosa with hypertension.[57]

There still has not been a very great experience with the hormonal therapy of dermatomyositis. The symptomatic or supportive measures as indicated in the first section of this report may be quite helpful. As with the other conditions, hormonal therapy appears to be most effective in earlier cases before extensive vascular and connective tissue changes have occurred.[14,48,50] Prolonged remission after therapy is unusual and relapses common. Some of the patients with a primarily polymyositic dystrophic-like syndrome have shown a significant response, but this may take six to eight weeks with a dosage of 100 mg. per day, even though improvement in cutaneous and constitutional manifestations occur within one to two weeks. Physical therapeutic methods to prevent contracture then may be of prime significance. Para-aminobenzoic acid has given variable and disappointing results and is not recommended because of prominent toxic effects. Some workers have suggested the use of testosterone propionate given intramuscularly or by pellet implantation. The dose has been 50 mg. intramuscularly in oil twice weekly, or three to four pellets of 100 mg. each implanted. The results are supposed to be better after a course of cortisone or ACTH, but in general this therapy is not regarded as too promising.

The results of therapy in scleroderma are still very equivocal. Cortisone and ACTH have been used in addition to general supportive measures and the reports have ben quite variable.[16,32] In some patients a suppressive effect has been observed, in others no change has occurred, and in some cases an actual aggravation of symptoms has developed. The use of vasodilating drugs such as Priscoline and Etamon for the Raynaud's phenomena has not been too effective. Similarly sympathectomy has not been reported to be particularly helpful except in a few instances with upper body involvement.[16] The response following sympathetic nervous system suppression either by pharmacologic blockade or sympathectomy has usually been transient because of the actual progression of the disease process involving the small peripheral blood vessels.

NEUROLOGIC COMPLICATIONS OF CORTISONE AND ACTH THERAPY IN COLLAGEN DISEASES

The basic problem relating to these complications is that the many varied manifestations of these diseases and the complications resulting from hormonal therapy may simulate each other quite closely. Of special importance neurologically is the occurrence of convulsions, psychotic mental states, and asthenic reactions. The other significant complications are: specific obesity, "moon" facies and plethoric appearance, hypertension, peripheral edema with weight gain, unusual susceptibility to infection, gastrointestinal tract ulceration, poor wound healing, purpura or easy bruising, acneform dermatitis, impotence in males, menstrual disturbances and hirsutism in females, polydipsia or polyuria, glycosuria, and osteoporosis.[13, 25,26,52,59] Most patients under treatment with these hormones develop these as physiologic side effects of prolonged hyperadrenalcorticalism, which are actually similar to the signs and symptoms of Cushing's syndrome.[41] Recently another type of reaction associated with chronic hypercortisonism has been observed[51] in treated patients with rheumatoid arthritis, especially just following cortisone withdrawal. Postmenopausal women are particularly predisposed. In these cases diffuse panmesenchymal and panangiitic reactions occurred, associated in many instances with positive L.E. cell tests. The clinical picture, therefore, resembled an induced systemic lupus or periarteritis. However, as discussed above, frequently an exacerbation or rebound of systemic lupus may occur after hormone withdrawal, and it is quite possible that these patients had a systemic lupus previously manifested only by arthritis. In addition, it should be mentioned that exacerbations of collagen diseases, especially systemic lupus, may be triggered by an allergic drug reaction[25] and that this has been described with ACTH, penicillin, sulfonamides, streptomycin, Chloromycetin, Aureomycin, gold salts, quinine, and para-aminobenzoic acid. Hypersensitivity reactions have been causative predominantly in periarteritis nodosa.[17,31] Therefore great care must be exercised in giving any drugs to these patients.

In the background of the drug effects is the relatively high incidence of convulsive seizures and organic psychotic reactions related to cerebral lesions occurring during the natural course of the collagen disorders. A high occurrence of subclinical central nervous system involvement has been shown by the findings of abnormalities in the electroencephalogram, psychologic tests, and cerebrospinal fluid in cases with very little symptomatic nervous system involvement. However, both seizures and abnormal mental reactions may be induced by these hormones in the treatment of other disease states which are not predisposed to central nervous system lesions.[5,6,18,20,23,44,55] Therefore, when these manifestations occur during the course of treatment, it is often very difficult to determine whether the reactions are due to the disease process itself or are actually induced hormonally. Occasionally there does not seem to be any relationship to the general response of the patient since these neurologic complications may occur during a phase of systemic improvement. It has been stated that these reactions are more likely to be due to active collagen disease lesions if the patient has had a recent exacerbation and is febrile, normotensive, and

has not had a history of recent weight change.[13] The complications are more likely due to treatment if they occur late in the course of treatment, especially when the Cushing's state is marked.[13] In the latter cases fluid retention, hypertension, and potassium deficiency may be significant factors in the production of these reactions in the central nervous system. In the great majority of instances, however, seizures or abnormal mental states are not correlated with changes in fluid balance, blood pressures, or serum electrolyte levels and are not helped by administration of potassium.[4,5,9,20,21,25,42]

Both ACTH and cortisone have been reported to have induced or been associated with the onset of convulsive seizures in patients with periarteritis nodosa,[8,9,46] systemic lupus,[9,13,,52,53] and dermatomyositis.[7,9] The relationship between alterations of adrenocortical activity and the convulsive state has been reviewed in detail recently,[21,62] and there is now definite evidence that the hormones, especially cortisone, may lower the convulsive threshold and increase cerebral excitability or susceptibility to convulsions. In addition, it has been determined that both prolonged and acute administration of these hormones may induce variable electroencephalographic abnormalities,[9,22,27,39,56,61] particularly an increase in theta activity, and in certain instances an enhancement of bilateral spike-wave discharges in epileptic subjects. These changes have led to the suggestion that there may be a direct effect of these hormones on deeper, subcortical diencephalic structures.[56] As already stated, these changes are usually independent of alterations in serum electrolytes. Intracellular electrolyte concentrations in the brain are apparently independent of marked changes in serum concentration, but it has been determined that the excitability of the cerebral cortex varies inversely with the serum sodium and directly with brain sodium concentrations.[62] Also it has been found that adrenal steroids produce no significant changes in cerebral blood flow or carbohydrate metabolism with the usual therapeutic dosage levels. It has been concluded that cortisone and related oxysteroids may act upon brain excitability without influencing brain or plasma electrolytes significantly.[62] Also, there is the possibility that corticotropin or ACTH possibly may produce changes in the electroencephalogram by a direct effect upon cerebral electrical activity.[22] Yet the basic mechanisms of these changes in the electroencephalogram and the production of seizures are still not clear. Further direct investigations of electrolyte distributions and shifts within brain substance are indicated. In addition, the significance of hormonally induced changes in the electroencephalogram with regard to actual brain function is not certain. Although in a few instances there has been the association of change in the electroencephalogram with the occurrence of psychosis, this correlation is not usually present. In the case of collagen disorders with brain lesions already present, a lowered convulsive threshold produced by these hormones may make seizures more likely to occur. It is of interest, however, to realize that although the electroencephalogram has worsened in some cases and seizures have appeared in others, the electroencephalogram occasionally may be improved by hormonal therapy.[39,45] There is no convincing evidence that hormonal therapy really improves seizure states in systemic lupus.[13,25] It is

felt that in most instances the seizures are actually due to the basic disease process, and there is the general feeling that incidence increases during hormonal therapy. Death in status epilepticus during hormonal therapy has been reported. In one series, 30 per cent of the patients were regarded to have seizures due to systemic lupus lesions, and an additional 5 per cent developed seizures as a result of hormonal treatment.[13] In most series convulsive seizures occurred in a terminal or preterminal phase of the disease. The appearance of seizures as a manifestation of the basic disease process is no absolute contraindication to hormonal therapy, however. Also, when seizures occur as a complication of hormonal therapy in the absence of other neurologic symptoms, it may be advisable to continue therapy if the patient is having a good general response, with an attempt to control the seizures by proper anticonvulsant medication (phenobarbital and Dilantin).

An important contributing factor in the neurologic and other complications may be the occasional hypertensive effect of these hormones, especially in patients with renal damage.[38] Recently, there have been reports of severe hypertension with encephalopathy (often hemorrhagic) developing in patients with collagen diseases treated with ACTH and cortisone.[13,15,18,47]

Extensive literature has accumulated over the past five years concerning the occurrence of abnormal mental states in association with the administration of the hormones ACTH and cortisone.[2,5,6,20,23,42,44] Again, similar to the problem of the convulsive states, there is the difficulty of evaluating whether the reaction is due entirely to the basic disease process or to the effects of the hormones. Most case series indicate a rather high incidence of abnormal psychologic reactions in patients with collagen disease. For example, at least 30 per cent of patients with systemic lupus have these reactions, especially during acute exacerbations. It has been estimated that these tend to increase markedly during the course of hormonal therapy, up to as high as 60 per cent in one series.[52] However, there are instances of improvement in abnormal mental states when these are due to actual cerebral lesions of the disease process.

The over-all occurrence of psychotic reactions induced by hormones in the treatment of various medical illnesses has not been determined completely, although it can be estimated at about 5 per cent in some series.[20,23] In patients with collagen diseases this may increase to possibly over 20 per cent.[13,25,53] The manifestations of these psychotic reactions vary a great deal and the following wide range of disturbances have been observed:[2,5,6,20,23,44] affective changes with elevation or depression of mood, depressive, grandiose, or paranoid delusions, perceptual disorders with hallucinations and illusions, depersonalization and disordered body image, manic reactions with flight of ideas, pressure of speech, overactivity and aggressiveness, mutism and immobility, turmoil states, impaired memory, confusion, and disorientation. Similar mental changes have been described in patients with Cushing's syndrome.[20,54,60] Attempts at classification are difficult and controversial, but two general patterns may be stated to occur:[20] a primarily affective disorder, elated or depressive, and a more complex reaction with "organic" components and associated paranoid-hallucinatory and affective (usually de-

pressive) features. These latter reactions are associated with a delirial state which may be mild, with defects in memory and in other components of sensorial functions. Predisposing abnormal personality patterns may be significant but do not always presage the development of psychotic reactions with these treatments, since many patients have developed these reactions in a previously normal personality setting. The manic reactions seem to develop within several days from the start of treatment. These reactions begin with a feeling of well-being, usually due to relief of chronic disabling symptoms, especially pain and immobility. Sensations of euphoria and elation then may appear, and it is very difficult to determine whether this heightened affective state is a purely reactive psychologic response or a metabolic result. The patients develop irritability, tension, insomnia, and aggressive tendencies. In some cases severe psychotic depressive reactions occur. Difficulties in clinical management may appear rapidly in the manic patient. Once the hormone is discontinued, the mental disturbance usually ceases gradually within a few days. In some instances, however, a full manic storm once started may increase in severity even after the cessation of treatment. In some cases assaultiveness, suicidal tendencies, physical exhaustion, and severe depression have led to the use of electroconvulsive therapy, and this has terminated the psychosis effectively without adversely affecting the basic collagen disease.[20] The more complex psychotic reaction with organic features may resemble a schizophrenic or schizoaffective state. These reactions may appear at any time during the treatment and have no constant relation to dosage. They have had an extremely variable duration, in one series from one to 35 days after cessation of hormone therapy.[20] Spontaneous remission usually occurs after the hormone is discontinued. Certain patients were found to have had psychotic tendencies prior to treatment but not all. Here, as in any organic psychotic reaction, the previous personality pattern determines the content of psychotic productions. Only in a small percentage of cases was there any correlation between the occurrence of electroencephalographic abnormalities and these psychotic reactions. However, in some instances the occurrence of mental disturbance was a prelude to a severe convulsive episode.[9]

There are as yet no entirely satisfactory explanations concerning the mechanisms producing these mental disturbances. Recently the many possibilities and hypotheses have been reviewed thoroughly and critically.[42] It is felt that the important primary factor involved is the modification of central nervous system function as a physiologic effect of the hyperadrenal state.[20,42] This is the basic change in every patient treated, but does not account for differences in susceptibility or patterns of behavior. The other more predisposing, precipitating factors and those which determine specific clinical features[2,20,23,42,44] are: physical differences increasing susceptibility to the above, such as cerebral lesions or metabolic changes due to the underlying disease; previous personality patterns of adjustment, including psychotic potentialities; and specific situational features relating to the patient's psychologic reaction to his disease and its treatment, especially the removal of psychologic defenses by relief of symptoms.

In these patients with the development of psychotic reactions, there is again the problem of whether or not the hormone should be discontinued. It is known that stopping the hormone often allows the psychotic reaction to abate. However, this may not occur for several days or even weeks. On the other hand, if the psychosis is due to an acute exacerbation of the collagen disease, as often occurs in systemic lupus, more treatment is indicated. Therefore, if there are suggestions clinically of the presence of an acute exacerbation of the disease process, it may be advisable to increase the dosage of hormone for several days in an attempt to bring the basic disease under control and determine whether or not this has any effect on the psychotic reaction. If this is not successful, careful slow hormone withdrawal is necessary.

The complication of severe mental disturbances during hormonal therapy raises the question of selection of patients for therapy and the related problem of the desirability of resuming treatment after a psychotic upset has subsided. These decisions depend to a great extent on the clinical severity of the somatic illness and whether it is felt that the expected response to the hormones would warrant the risk of inducing another psychosis. Several patients have been retreated after such a psychosis, some successfully. It has been determined that these psychotic reactions are mostly either self-limited after hormone withdrawal or amenable to electroconvulsive therapy. However, there is the danger of suicide, especially in the depressive reactions, and the possibility of a prolonged psychotic illness in the other groups. Since not all patients who develop psychotic reactions have recognizable psychotic potentialities prior to the development of their disease or prior to therapy, effective selection would be extremely difficult.

In addition to the above major reactions involving the central nervous system, the administration of ACTH and cortisone to patients with these collagen disorders and other illnesses may produce a mild to moderate intermittent muscular asthenia[50] which is either generalized or confined to the lower extremities. This is a relatively common symptom in Cushing's syndrome.[41] The incidence is extremely variable and is in contrast to the occasional feelings of increased muscular strength which may be induced in some patients with dermatomyositis. In evaluating this reaction it has been determined that there are no significant concomitant changes in the serum electrolytes (such as a lowered potassium) which suggest the origin of the symptoms. It has not been altered significantly by the administration of large amounts of potassium salts. Asthenia may also occur after the withdrawal of cortisone[51] and then is symptomatic of the suppressed state of adrenocortical function. This withdrawal asthenia does not usually develop after the cessation of ACTH administration. In some patients during the period of hormone withdrawal there also may be increased signs of mental depression and irritability. For these and other reasons, slow withdrawal of hormones is recommended.

SUMMARY

The neurologic manifestations of certain collagen diseases – systemic lupus erythematosus, periarteritis nodosa, dermatomyositis, and scleroderma – have been reviewed with particular emphasis upon prognosis and therapy. The meth-

ods and results of acute and long-term treatment, especially with the hormones cortisone and ACTH, have been presented both in relation to the general disorder and the neurologic manifestations. The problems concerning the occurrence of complications such as seizures, abnormal mental states, and asthenia were reviewed with regard to mechanisms, diagnosis, and considerations concerning continued therapy.

It was emphasized that the present concepts of these diseases include a natural history in each which may be extremely variable, with spontaneous exacerbations and remissions often lasting long periods of time. It was pointed out that these factors make the evaluation of therapy extremely difficult. The most effective treatments available at present, however, are the hormones cortisone and ACTH, but these treatments are only suppressive in nature and not biologically curative. These hormones induce the profound metabolic and systemic changes of the hyperadrenal state of Cushing's syndrome and must be administered with great care.

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A Study of Free Amino Acids In the Human Cerebrospinal Fluid

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THE FIRST chemical investigations of the cerebrospinal fluid, as well as the first recorded spinal puncture, were credited to Quinke in 1891. Subsequent studies on the significance of cell count and quantitation of sugar and protein by this investigator clearly demonstrated the clinical value of the determination of the cerebrospinal fluid contents. Since that time little progress has been made in the analysis of other spinal fluid constituents capable of providing aids to the diagnosis of nervous system disease. Many of these constituents may be altered in the presence of nervous system pathology. Among these substances are the free amino acids which, like the blood free amino acids, arise from absorption, synthesis, and tissue breakdown. They thus contribute to the free amino acid pool from which amino acids are continually withdrawn for the synthesis of tissue proteins and other nitrogenous compounds, as well as for energy-yielding oxidation. Alterations in the metabolism of amino acids, particularly the essential amino acids, will lead to a disturbance in tissue synthesis. Furthermore, abnormal tissue breakdown may change the normal amino acid turnover.

It can be assumed, therefore, that such disturbances may be reflected in the free amino acid pool of blood and cerebral spinal fluid. Amino acid changes in blood have been demonstrated under various pathologic and experimental conditions. However, alterations in the amino acid content of the spinal fluid have never been clearly elucidated. The assumption that cerebral metabolic changes may manifest themselves by changes in the free amino acid content of the cerebrospinal fluid is an attractive hypothesis, since gross protein changes may occur in the spinal fluid in cases of central nervous system disease without demonstrable changes in plasma proteins. Amino acid alterations could then be employed as a diagnostic aid as well as in the study of the metabolism of the disease in question.

The tedious and frequently inaccurate laboratory procedures necessary to the separation and quantitation of amino acids resulted in the neglect of these studies in body fluids for many years.

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With the development of paper chromatography,[1,2] a simple analytic tool was provided for the study of amino acids.

PRINCIPLES OF THE PAPER CHROMATOGRAPHIC TECHNICS APPLIED TO AMINO ACIDS

Essentially, paper chromatography consists of the application of a small drop of the solution, containing the free amino acids to be separated, to a strip of filter paper a short distance from one end. When the amino acid concentration is low, large volumes of fluid are required. Consequently, several drops must be applied to a single spot and sufficient time must be allowed for drying between applications. Following the application of the fluid, the end of the paper containing the spot is immersed into a developing solution, usually a water containing organic solvent. This solvent flows past the "spot" by capillary action and the amino acids are separated along one dimension. The position taken by each amino acid depends upon its partition between the water and the solvent phase, as well as upon absorption and ion exchange factors.

After the solvent has run a convenient distance, the paper is removed, dried, and sprayed with a developing reagent such as ninhydrin. The amino acids then appear as colored spots taking a more or less constant position on the paper. The recognition of each amino acid on the paper is accomplished by studying the pattern of the amino acid spots, by determining the Rf values, and by employing such acids as markers. The Rf value represents the ratio of the distance run by the amino acid and the distance traveled by the solvent. This Rf value is quite constant for each amino acid.

More recently two dimensional chromatography has been developed, thus allowing a better resolution of the amino acids. In this procedure the paper strips are replaced by squares. The amino acids are separated as in one dimensional procedures and then are further separated by a second solvent at right angles to the first run. The substances then appear as colored spots covering the whole plane of the paper.

The colored spots thus obtained can be subjected to quantitative analysis. Among the most popular quantitative procedures are the elution of each spot, followed by spectophotometric determination, and the direct measurement of the color density of each spot on the paper by means of a densitometer.[3]

Although the analysis of simple mixtures of amino acids is relatively easy, the complexity of body fluids necessitates special treatment prior to spotting in order to remove interfering substances such as proteins and salts.

APPLICATION OF PAPER CHROMATOGRAPHY TO SPINAL FLUID ANALYSIS

The chromatographic method described above has been found readily applicable to plasma and urine, and extensive studies of these fluids have been reported in both health and disease. However, the analysis of spinal fluid has proved to be more difficult and studies have consequently been limited. Among various difficulties the greatest arises from the relatively small concentration of the amino acids present in this fluid. In order to carry out a satisfactory analysis, approximately 1 ml. of cerebral spinal fluid must be employed. This volume is eight times that of plasma or 40 times that of urine required to carry out a similar study. If the accepted meth-

ods of chromatographic analysis are employed, the entire 1 ml. of fluid must be spotted manually, utilizing few microliters at each application so that the separated amino acid spots are well defined and do not overlap. Sufficient time for drying must be allowed between the successive applications. This would require a minimum of 200 manual applications with a five microliter pipette and would thus necessitate a minimum of six hours of continual manual application of the material. If the study is to be quantitative, then each drop must not exceed 2.5 microliters, thus 400 manual applications and 12 hours of work are required.

Attempts to overcome this problem have been made by completely drying the fluid and rediluting in 0.25 ml. of distilled water, but have failed to provide the proper solution. This situation results because the procedure of concentration itself may produce a considerable error; certain amino acids of lower solubility may be only partially redissolved in the small final volume. Considerable amounts of the amino acids to be analyzed may also be lost on the wall of the flask containing the small final concentrated specimen. A considerable loss of several amino acids was demonstrated in this study during attempts to concentrate the fluid to one-fourth of its original volume. An additional source of error in this procedure is the possible degradation of amino acids when high temperatures are employed to hasten drying in order to diminish the time necessary for manual spotting.

Because of these technical difficulties, chromatographic analysis of amino acids in the cerebrospinal fluid have been limited to a small number of largely qualitative studies. Solomon,[4] in 1947, became the first investigator to report quantitative studies when he listed values for 11 amino acids in the cerebrospinal fluid. His study was based on the microbiologic assay analysis of 16 specimens obtained from patients with various organic nervous system disorders.

Scattered reports of the purely qualitative analysis of amino acids by paper chromatography in a small number of normal and abnormal cerebrospinal fluid specimens have appeared in the literature.[5–10] The majority of these studies have shown a limited number of these acids. Walker, however, succeeded in consistently isolating nine amino acids, as well as seven additional amino acids in a less consistent fashion.[11] In two studies by Kemali[12–14] and Torre,[15] quantitative results were published in normal cerebrospinal fluid. The first investigator included three, and the latter a total of 11 amino acids. However, little attempt was made to demonstrate consistent changes in the pattern accompanying nervous system disease. Tinelli[16] reported an increase in tyrosine, phenylalanine, and tryptophan in schizophrenics. Rossi[17] noted an increase in glycine, alanine, valine, leucine, glutamine, and cystine in cases of tuberculous meningitis. Pond, however, failed to demonstrate any changes in a group of 25 neuropsychiatric cases.[5]

Because of the limitation in information concerning spinal fluid free amino acids, the present investigation was aimed at the survey of a large number of normal and pathologic fluids.

MATERIAL AND METHODS

The initial phases of this investigation were devoted to modification and simplification of the available chromatographic technics in order to permit the

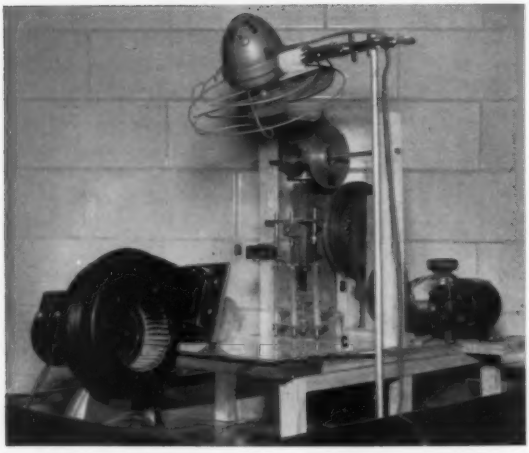

FIG. 1. The spotting apparatus. The syringes containing the spinal fluid are seen attached to the device. The plungers of the syringes are periodically depressed upon engagement of the gear (A) by the cog (B). Three squares of filter paper (C) covered by glass are exposed only at the point of delivery of the fluid. The electrical microswitch (D) will turn off the system upon delivery of the whole fluid.

study of a large number of specimens in a reasonable period of time. The manual application of the drops, which has been the principal source of difficulty, was overcome by developing an automatic procedure allowing the use of at least 1 ml. of fluid spotted directly on the paper. The spotting apparatus (figure 1) is simple in construction and operation. It does not require supervision while operating, it may carry many specimens simultaneously, and it completely avoids heating of the paper. This machine intermittently delivers drops of spinal fluid which have previously been desalted and deproteinized. This material is applied to chromatographic paper in aliquots of 1.5 microliters. This is accomplished by taking up the desalted deproteinized fluid in three tuberculin syringes attached to the mechanical device. The rotation of gears on this device allows each plunger to be periodically depressed a constant distance and results in the deposition of a single small drop in the corner of each paper. The aliquot is then dried by an air current before the succeeding drop is deposited. Since the preparation of this paper, suction through circular holes in the mounting beneath the paper has been found to be a more satisfactory drying procedure and has replaced the fans. This technic allows processing of three spinal fluid samples simultaneously and automatically in a period of approximately eight hours. The apparatus requires only a few minutes to set up, in contradistinction to the many hours of manual spotting necessary by previous technics. The spotted paper is then processed in the routine manner previously described by two-dimensional chromatography.

An additional acceleration in the procedure was made possible by modifying the electrolytic desalting apparatus of Consden.[18] This apparatus consists essentially of a circulating mercury anode, a carbon cathode, and a chamber containing the fluid to be desalted. The modified apparatus may be seen in figure 2, in which the single chamber has been replaced by five such chambers arranged

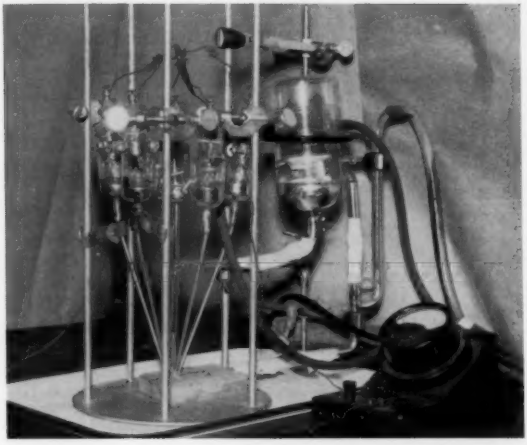

FIG. 2. The modified electrolytic desalting apparatus. The five desalting chambers (A) contain the individual spinal fluid specimens (B) floating on the mercury (C).

in a concentric fashion, thus allowing the simultaneous desalting of five specimens in approximately the identical time previously required for a single procedure.

The above described modifications now permit the analysis of approximately 22 duplicate spinal fluid specimens weekly. This may be contrasted to the four to five analyses possible by the employment of the manual method. It is anticipated that modifications now being carried out on the spotting apparatus will allow a four-fold increase in the number of specimens processed by this procedure.

RESULTS AND DISCUSSION

Qualitative Data

Utilization of the described technics has allowed the study of 210 spinal fluid specimens in duplicate or triplicate analyses from different individuals with normal and malfunctioning nervous systems.

The amino acids were identified on the paper by comparison of the relative position of the spots and the individual Rf values, with similar values previously obtained from the average of 50 standard runs employing pure amino acids. Development of known amino acids was always carried out for reference simultaneously with the unknown run. A total number of 18 free amino acids were identified. Among these, eight were present in over 85 per cent of the cases and included aspartic acid, alanine, glutamic acid, glutamine, glycine, leucine, serine, and valine. The remaining ten amino acids were present less consistently and included: alpha-amino-butyric acid, gamma-amino-butyric acid, lysine, phenylalanine, proline, threonine, tyrosine, arginine, histidine, and cystine.

The over-all qualitative results in this study are compared in table 1 with the results previously reported by other investigators. The number of amino acids observed by Walker are in essential agreement with those demonstrated in the present study. The limitation in number of amino acids in all remaining studies appeared to result from the utilization of small volumes of fluid, as well

TABLE 1
OCCURRENCE OF AMINO ACIDS IN HUMAN CEREBROSPINAL FLUID

	Solomon et al. 1947	*Boulanger et al. 1949*	*Pond 1950*	*Kemali et al. 1952-53*	*Shönenberg 1953*	*Torre et al. 1953*	*Reitman et al. 1954*	*Walker et al. 1954*	*Logothetis 1955*
Number of cases examined	16	"few"	25	25	"few"	10	30	?	210
Aspartic acid		•		•				•	•
Alanine		•	•	•	•	•	•	•	•
Arginine	•			•		•		•	•
A-amino acid									•
Asparagine									?
Cysteine-cystine	•			•		•			•
Glutamic acid		•	•	•		•	•	•	•
Glutamine			•	•			•	•	•
Glycine		•	•	•		•		•	•
G-amino-butyric acid							•	•	•
Histidine	•			•		•			•
Lysine	•				•			•	•
Leucine	•	•	•	•	•	•		•	•
Methionine	•								
Ornithine								•	
Proline								•	•
Phenylalanine	•			•		•		•	•
Serine		•		•?				•	•
Tryptophan						•	•		
Threonine	•							•	•
Tyrosine	•			•		•		•	•
Valine	•	•	•	•		•	•	•	•
Total number amino acids reported	10	7	6	12+1?	3	11	6	16	18+1?

as possible loss resulting from the use of complex chemical procedures.

Some of the variations between Walker's study and that of the present investigation are of interest. Walker consistently demonstrated gamma-amino-butyric acid, while this finding was inconsistent in our investigation. The consistency of gamma-amino-butyric acid has also been questioned by Harman in a brief discussion of Walker's paper. In the present investigation, leucine was noted consistently while phenylalanine was variable. Walker's findings were just the reverse. This discrepancy might have arisen because of the proximity of the Rf values of these two amino acids. Alpha-amino-butyric acid has not been noted in any previous report. However, this amino acid was observed in a small percentage of normal and abnormal cases in this investigation. In contrast to Walker's study, ornithine was not demonstrable, whereas cystine and histidine were found in a limited number of fluids.

Quantitative Data

Following the identification of the amino acid spots on the paper, the technic of maximum color density[3] by the use of a densitometer was employed for the measurement of the densities corresponding to each amino acid spot. The concentration in millimoles or micrograms per cc. was then obtained by using prepared calibration curves obtained from known mixtures of amino acids. To obtain the standard curve of each acid, the mean optical densities of 25 replicate analyses at 1, 2, 4, 6, 8, and 10 millimolar concentrations were plotted on graph paper.

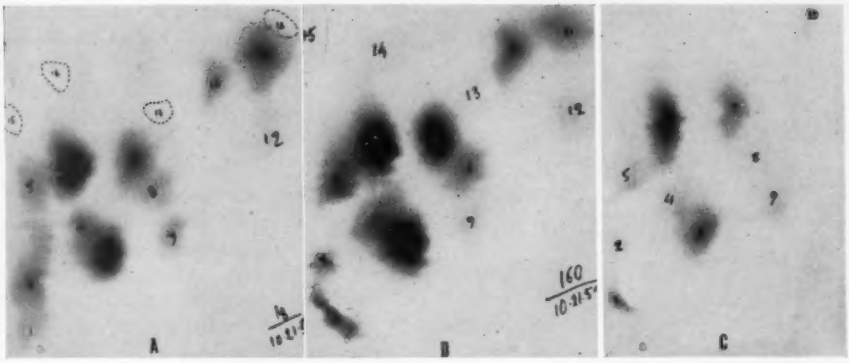

FIG. 3. Amino acid chromatographic patterns of human cerebrospinal fluid: (A) normal, (B) hereditary cerebellar ataxia, (C) multiple sclerosis. The individual amino acid spots represent: 1. Aspartic acid; 2. Glutamic acid; 3. Serine; 4. Glycine; 5. Lysine; 6. Glutamine; 7. Alanine; 8. Threonine; 9. Taurine (added as internal standard); 10. Valine; 11. Leucine; 12. Tyrosine; 13. A-aminobutyric acid; 14. Gamma-aminobutyric acid; 15. Arginine. Dotted areas represent amino acids found in some of the other normal cerebrospinal fluids analyzed.

Normal series: Fifteen free amino acids were identified in 17 normal spinal fluids obtained from patients undergoing spinal anesthesia. All patients were free of any neurologic disorder or systemic disease. The demonstrated amino acids include: aspartic acid, glycine, lysine, serine, glutamine, alanine, threonine, valine, tyrosine, glutamic acid, leucine, gamma-amino-butyric acid, alpha-amino-butyric acid, phenylalanine, and arginine (figure 3A).

The quantitation of amino acids in the normal cerebrospinal fluid and the incidence of occurrence of each amino acid are tabulated in table 2.

Abnormal series: Although 17 cases are an insufficient number to completely establish normal values, they are useful at present to serve in the comparison with the quantitative values observed in instances of disease of the nervous system. Amino acids previously noted in the normal series were identified, as was proline, histidine, and cystine. One hundred ninety-three specimens were examined in which there was clinical evidence of nervous system pathology. The

TABLE 2

AMINO ACIDS IN THE NORMAL CEREBROSPINAL FLUID BASED ON 17 CASES

	Aspartic acid	*Alanine*	*Arginine*	*Alpha-aminob. ac.*	*Glycine*	*Glutamic acid*	*Glutamine*	*Gamma-aminob. ac.*	*Lysine*	*Leucine*	*Phenylalanine*	*Serine*	*Tyrosine*	*Threonine*	*Valine*
	Micrograms per milliliter of spinal fluid														
Mean	1.5	1.8	1.2	.2	1.4	1.4	3.0+	.2	1.9	1.2	1.8	2.5+	.8	1.4	1.0
Pct. occurrence	100%	86%	28%	14%	90%	70%	100%	20%	70%	86%	24%	95%	67%	70%	95%
S. D.	±.9	±.7	±.7	±.2	±.4	±.6	±1.2	±.1	±1.2	±.3	±.2	±.8	±.5	±.9	±.6

TABLE 3
SURVEY ANALYSIS OF SPINAL FLUIDS FROM PATIENTS WITH NERVOUS DISORDERS

Convulsive disorders	35
Central nervous system lues	12
Encephalitis	8
Myelitis	6
Neuritis	5
Multiple sclerosis	9
Degenerative brain disease	13
Degenerative cord disease	7
Brain tumor	5
Cord tumor	3
Presenile psychosis	6
Schizophrenia	8
Cerebrovascular disease	8
Miscellaneous group	68
Total	193

diseases included in this series are tabulated in table 3.

The majority of these analyses did not show conclusive evidence for consistent amino acid changes. However, definite changes were noted in the two cases of hereditary cerebellar ataxia examined, in which there was a general tendency for all amino acids to increase. This is demonstrated in figure 3B where the density of the amino acid spots in one of these cases can be grossly compared with the normal chromatograms in figure 3A. The study of the spinal fluid in eight cases of multiple sclerosis showed most amino acids in decreased concentration as indicated by the diminished density of the chromatographic spots (figure 3C). In six cases of presenile psychosis with demonstrable atrophy in the pneumoencephalogram, a universal reduction of the amino acids was noted.

The aspartic acid increase in cerebellar ataxia, the decrease in tyrosine and aspartic acid in multiple sclerosis, as well as the decrease in alanine and glycine in presenile psychosis were found to be significant by statistical analysis (figure 4). Some other observations con-

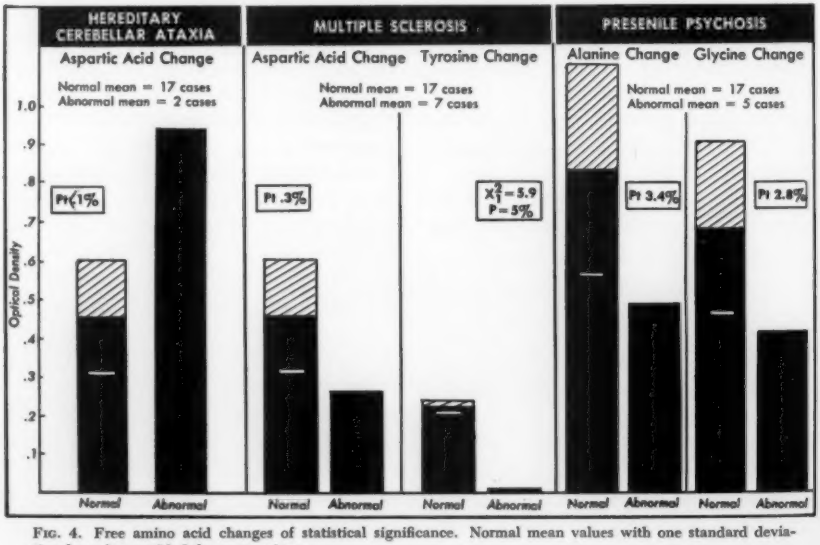

FIG. 4. Free amino acid changes of statistical significance. Normal mean values with one standard deviation have been added for comparison.

cerning alterations of spinal fluid amino acids and the nervous system disease have been made, but the number of cases studied are insufficient to establish the statistical validity of the observations. The suggested changes include the diminution in serine and arginine in albinism and some possible alterations in tabes dorsalis and in Huntington's chorea.

This investigation represents the preliminary steps in the study of free amino acids in the spinal fluid and the first reported attempt to quantitate free amino acids in a large number of normal and abnormal fluids.

The alterations in amino acid content of cerebrospinal fluid in central nervous system disease suggests changes in the metabolism of nervous tissue. The exact significance of these changes cannot be determined on the basis of this report. However, the establishment of the technic of paper chromatography for cerebrospinal fluid and the preliminary studies of pathologic changes in this fluid may lead to better understanding of amino acid metabolism of the nervous system in health and disease.

SUMMARY

1. The tedious procedure of paper chromatography of the cerebrospinal fluid has been modified to allow rapid, accurate routine identification of the constituent amino acids. This has been accomplished by modifying the desalting apparatus of Consden and developing an apparatus for the automatic concentration of spinal fluids in a small spot on chromatographic paper.

2. Multiple analysis of the amino acids in normal cerebrospinal fluid has permitted the identification and quantitation of 15 amino acids, including aspartic acid, alanine, arginine, alpha-amino-butyric acid, glycine, glutamic acid, glutamine, gamma-amino-butyric acid, lysine, phenylalanine, serine, tyrosine, threonine, valine, and leucine.

3. The analysis of 193 specimens of cerebrospinal fluid from patients with central nervous system disorder has demonstrated three additional amino acids, including proline, histidine, and cystine. Statistically significant alterations in the free amino acid content were noted in cases of hereditary cerebellar ataxia, multiple sclerosis, and presenile psychosis. Suggested changes were present in albinism, Huntington's chorea, and tabes dorsalis.

4. It is anticipated that further studies will demonstrate amino acid alterations in the cerebrospinal fluid of other central nervous system diseases.

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■ After having divided transversely a lateral half of the spinal cord in the dorsal region, if we divide longitudinally this organ, so as to separate its two lateral halves one from the other, and at a right angle with the transversal section, we find that sensibility persists in the segment partly separated from the rest of the cord, if it is not more than two inches long, in a large mammal, whether the longitudinal section has been made below or behind the transversal one, or above or before this transversal division. If the longitudinal section is more than two inches long, it is not sensitive in all its length. When there are three pairs of nerves attached to it, the one nearest to the transversal section is hardly able to give slight sensations; the next is a little more sensitive, but much less than in a normal condition; and the third is very sensitive, though not so much as the others on the same side and behind it. With a segment attached to the cord by its upper extremity, similar results are obtained, and it seems certain, both from these facts and from many others which it is not necessary to mention, that the decussation of the conductors of the sensitive impressions in the spinal cord, whether they are, at first, descending or ascending, takes place at a short distance from the point of insertion of the posterior roots.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Effect of Barbiturates on Latent Motor Deficits

Paul Teng, M.D. and Morris B. Bender, M.D.

AMOBARBITAL SODIUM (Amytal sodium) has been used not only as a hypnotic and sedative, but also as an agent to elicit anamnestic data which could not be obtained in ordinary clinical interview of psychiatric patients. It is known that parenteral injections of sodium Amytal produce changes in the psychic and emotional state of subjects.[1] Linn and Stein[2] found that aphasia is lessened, while Bergman and Green[3] demonstrated that aphasia became more conspicuous under the influence of barbiturates. Weinstein and co-workers[4] found that intravenous subnarcotic doses of sodium Amytal induced organic mental syndrome in patients with brain disease.

In spite of the fact that barbiturates increase the threshold for pain, they are ineffective analgesics. The increase of pain threshold is proportional to the concentration of barbiturate in the blood. Anesthetic concentration abolishes responses to sensory stimuli. Concentrations lower than anesthetic doses bring out latent defects in perception, such as displacement, allesthesia, and exosomesthesia, particularly on double simultaneous stimulation, in patients with organic disease of the brain.[5] In normal adults subanesthetic doses of Amytal bring out latent perceptual patterns indicating certain regions of the body, particularly the hand, as being less sensitive to double simultaneous stimulation.[6] In a study of effect of Amytal on perception in lesion of the spinal cord, Shapiro and Feldman[7] found that seven of the 11 patients studied showed an increase in sensory defects following intravenous injection of the drug. A higher or more definite sensory level was usually elicited.

The barbiturates also induce motor changes consisting of slurred speech, ataxia of extremities, and nystagmus on ocular deviations. Conversely, the injection of sodium Amytal abolishes spontaneous nystagmus on forward gaze.[8,9] Other abnormal involuntary movement, such as tremor in parkinsonism, the dyskinesias of chorea, and dystonia, are either reduced or stopped by the intravenous injection of sodium Amytal.[10] However, it is curious that palatal myoclonus and myoclonic twitching in the extremities are not abolished. Induction of a monoplegia or hemiplegia has been observed with this drug. This occurred in a patient with a vascular lesion of the brainstem who showed no weakness in the limbs on repeated neurologic examinations, but while under a sodium Amytal subnarcotic state a complete flaccid paralysis of the left limbs became

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TABLE 1
NUMBER OF PATIENTS TESTED UNDER SODIUM AMYTAL INJECTION

Control group	36
Lesions other than tumors or of vascular origin showed motor weakness under sodium Amytal injection	11
Intracranial lesions did not show motor weakness under sodium Amytal injection	35
Patients with intracranial lesions showed obvious motor weakness before the injection of sodium Amytal	27
Residual paralysis of poliomyelitis	6
Motor weakness observed under sodium Amytal in brain tumors	18
Motor weakness observed under sodium Amytal in cerebrovascular disease	9
Cordotomy for pain	2
Total	144

apparent. After the effect of the drug had worn off, the strength of the left extremities fully returned.

This paper concerns the use of sodium Amytal as a test in eliciting motor deficits, particularly in extremities of patients with disease of the nervous system.

CASE MATERIAL

In this series 144 patients varying in age from 17 to 89 years were studied. Among these 144 patients, 36 were chosen as controls (tables 1 and 2) consisting of cases of herniated intervertebral disk of the lumbosacral spine, osteoarthropathy of the lower cervical vertebrae with no long tract signs, myasthenia gravis with no motor weakness in the limbs, herpes zoster, posttraumatic headache, essential hypertension, spasmodic torticollis, scirrhous carcinoma of the temporal bone with no intracranial extension, hiccup and fainting spells of unknown origin, and conversion hysteria.

The experimental group contained 106 patients with various neurologic conditions (tables 3 to 6) such as brain tumor, cerebrovascular disease, multiple sclerosis, diffuse cerebral degenerative disease, convulsive disorders, acute encephalitis, arteriosclerotic parkinsonism, cerebral trauma, chronic cervicothoracic osteoarthropathy with or without long tract signs, and other spinal cord lesions.

Seventy-five patients with intracranial or intraspinal pathology who showed no sign of, or minimal suspicion of, motor weakness were specially chosen for the sodium Amytal test. The remaining 33 cases, including 27 of intracranial tumor and six with residual paralysis after poliomyelitis, who already displayed definite motor weakness before the intravenous injection of sodium Amytal, were also tested. The results obtained are discussed and interpreted later.

SODIUM AMYTAL TEST FOR MOTOR POWER

Each patient subjected to this test was examined carefully before the injection of sodium Amytal, and special attention was given to the motor status. The patient was asked to stretch out his arms with palms up, fingers spread, and eyes closed while counting forward or backward from one to 50. Barré's test was used for the examination of weakness of the lower limbs. Whenever a motor weakness was present, there was a drift to the affected outstretched or raised limbs. The drift was considered signifi-

TABLE 2
CONTROL CASES

Herniated intervertebral disk, L5-S1	10
Osteoarthropathy, lower cervical, no long tract sign	6
Herpes zoster	2
Posttraumatic headache	2
Essential hypertension	1
Spastic torticollis	1
Tumor of the mastoid, no intracranial involvement	1
Hiccup	3
Fainting spell, cause unknown	2
Conversion hysteria	2
Myasthenia gravis, with no weakness in the limbs	6
Total	36

cant when the affected limb on one side fell at least several inches from the original position. If both the right and left extremity dropped an equal distance of several inches, it was not considered as a positive result. To elicit weakness of the face, the patient was asked to show his teeth or to smile. After the completion of sodium Amytal injection, the patient was examined again by the same procedure. In many instances the examiners were not informed of the clinical history, neurologic and laboratory findings such as x-ray of the skull, pneumoencephalogram or ventriculogram, arteriogram or electroencephalogram, in order not to influence their observation.

Sodium Amytal was given intravenously in a solution of 0.5 gm. in 10 cc. of distilled water at a rate of 0.05 gm. per minute. The injection was continued until the patient showed rapid nystagmus on lateral gaze in both directions, slurred speech, errors in counting backward, and drowsiness. These were regarded as indicators of the subnarcotic effect of Amytal. The total amount given to a patient depended on the appearance of a maximal effect of the drug. The total quantity actually used ranged from 0.1 to 0.5 gm. The injection was given slowly, and a large dose was avoided in order not to induce deep drowsiness which usually interfered with satisfactory interpretation of its effects.

RESULTS

In none of the 36 controls was a motor weakness elicited under sodium Amytal injection. Of the 30 cases with brain tumor, premedication neurologic examination revealed suspicious weakness or minimal to slight motor deficit in the corresponding side limbs and/or face in 11, while the remaining 19 cases showed no motor disturbance (table 5). However, under sodium Amytal, a conspicuous weakness of the central facial type and/or weakness in the arm or leg was found in seven patients who had shown no defects prior to the injection, and in 11 patients the motor deficit became more conspicuous, so that 18 of the 30 cases tested manifested motor deficits.

In 12 of the 30 cases of brain tumor, a motor disturbance was neither found before nor after the injection of sodium Amytal. This group consisted of one patient with craniopharyngioma, four with pituitary adenoma, two with neurofibroma of the eighth cranial nerve, two with cerebellar astrocytoma, one

TABLE 3
LESIONS OTHER THAN TUMORS OR OF VASCULAR ORIGIN SHOWED MOTOR WEAKNESS UNDER SODIUM AMYTAL INJECTION

Cerebral laceration, left parietal	1
Parkinsonism after unilateral pedunculotomy	1
Multiple sclerosis (bulbar involvement)	3
Convulsive disorder, cause undiagnosed	1
Acute encephalitis or cerebritis	1
Diffuse cerebral degenerative disease with cortical atrophy	1
Cervicothoracic osteoarthropathy (with long tract signs)	2
Amyotrophic lateral sclerosis	1
Total	11

with meningioma of the anterior fossa, and two with gliomas of the left temporal lobe.

The histologic diagnosis of those 18 cases of brain tumor in which a motor weakness had been elicited under sodium Amytal was oligodendroglioma in four, with one displaying malignant change, meningioma in four including one of malignant nature, glioblastoma multiforme in seven, metastatic carcinoma in two, and posterior fossa metastatic lymphosarcoma in one (table 5).

A motor weakness was found under sodium Amytal in nine of ten patients with a cerebral vascular lesion, including one involving the brainstem. In three of these ten patients, subsequent Amytal tests were repeatedly done during a period of six to 24 months after the disappearance of the motor weakness and the results were negative.

TABLE 4
INTRACRANIAL LESIONS WHICH DID NOT SHOW MOTOR WEAKNESS UNDER SODIUM AMYTAL INJECTION

Isolated 6th cranial nerve palsy, cause unknown	1
Craniopharyngioma	1
Pituitary adenoma	4
Multiple sclerosis	5
Parkinsonism	3
Neurofibroma, 8th cranial nerve	2
Cerebellar astrocytoma	2
Convulsive disorders, undiagnosed	3
Acute meningoencephalitis	1
Convulsive disorder, due to hypoglycemia	1
Psychomotor seizure	1
Uncinate seizure	1
Diffuse cerebral degenerative disease	2
Senile depressive psychosis	2
Cerebrovasclar disease	1
Transient diplopia, cause unknown	1
Posttraumatic epilepsy with left anterior frontal EEG focus	1
Meningioma, left frontal pole	1
Astrocytoma with anaplastic changes, left temporal lobe (normal EEG)	1
Glioblastoma multiforme, left temporal lobe, inferior	1
Total	35

Other subjects in which a positive Amytal test was obtained were three cases of multiple sclerosis with bulbar involvement, two cases of cervicothoracic osteoarthropathy with long tract signs, and single cases of convulsive disorder of unknown cause, acute encephalitis, parkinsonism after a unilateral pedunculotomy, amyotrophic lateral sclerosis, diffuse cerebral cortical atrophy, and traumatic laceration of the cerebrum (table 3).

Thirty-five cases of various intracranial lesions in which a motor weakness was not observed under sodium Amytal are listed in table 4. This includes seven with convulsive disorders, four pituitary adenoma, three parkinsonism, two diffuse cerebral degenerative disease, two senile psychosis, five multiple sclerosis, two cerebellar astrocytoma, two neurofibroma of the eighth cranial nerve, and one each of isolated sixth cranial nerve palsy of unknown cause, craniopharyngioma, acute meningoencephalitis, cerebrovascular disease, transient diplopia of unknown cause, meningioma of the left frontal lobe, astrocytoma of the left temporal region, and glioblastoma multiforme of the left temporal lobe.

In two patients who had cervicothoracic osteoarthropathy with long tract signs, the injection of sodium Amytal exaggerated the weakness in the affected limbs (table 3). In six cases of the same disease, but without long tract signs, the result of the sodium Amytal test was negative (table 2).

In six patients with residual weakness after poliomyelitis, intravenous injection of sodium Amytal did not alter the weakness. In 27 patients with verified tumor involving the frontoparietotemporal regions, the weakness in the affected limb or limbs was either unchanged or exaggerated, as listed in table 1.

Three cases are briefly presented to demonstrate the manifestation of motor weakness after sodium Amytal injection.

Case 1.—A 61 year old man was admitted to Mount Sinai Hospital on December 26, 1953, complaining of a bony mass on the right side of the skull where he had been hit by a wrench two years previously. Two months later he noted a hard and nontender lump about 1 cm. in diameter at the site of the previous injury. Since then this lump has continued to grow in size.

Physical examination revealed a large bony mass measuring approximately 5 by 7 cm. in the right parietal region close to the midline. Otherwise the physical and the neurologic findings were normal.

The laboratory findings showed normal cerebrospinal fluid and a normal electroencephalographic record. A skull x-ray revealed a soft tissue swelling in the right parietal region with marked enlargement of the diploe and some spicule formation.

On the tenth day of admission an Amytal test was done, and a definite left lower facial weakness was elicited. Subsequent pneumoencephalography revealed enlargement of both lateral ventricles with a depression of the roof of the right ventricle. Six days later a craniotomy was performed and a large meningioma was removed from the right parietal region close to the midline. Two weeks following the operation examination showed no motor deficit with the exception of a very fine tremor in the left hand. However, on this date, a sodium Amytal test again elicited a marked left lower facial weakness, and the tremor of the left hand became more obvious. The patient was discharged from the hospital a week later.

Comment: This patient showed no abnormal neurologic finding on repeated examinations. A sodium Amytal test brought out a left lower facial weakness, suggesting the possibility of right cerebral involvement. This suspicion was confirmed by subsequent pneumoencephalogram and craniotomy. The sodium Amytal test obtained the first clue as to localization of the cerebral involvement in this case.

Case 2.—A 62 year old man was admitted to Mount Sinai Hospital on May 22, 1954. Since 1946 the patient had had repeated attacks of

TABLE 5
POSITIVE RESULT OBTAINED IN CASES OF BRAIN TUMORS

Patient	*Age*	*Sex*	*Neurologic findings before sodium Amytal test*	*Motor weakness disclosed under sodium Amytal test*	*Final diagnosis and location of lesion*
S.M.	60	M	Focal seizures; inconsistent left lower facial weakness; suspicious drifting left arm; EEG right frontal and parietal focus	Obvious left lower facial weakness; definite drifting left arm	Oligodendroglioma, right frontoparietal region
J.M.	61	M	All neurologic findings normal; bony mass in right upper parietal region; EEG normal	Definite left lower facial weakness	Meningioma, right upper parietal region
			13th postoperative day; all findings remain normal	Definite left lower facial weakness	
S.M.	57	F	Organic mental syndrome; exaggerated deep tendon reflexes, right side; right Hoffman's sign, foot drop, slight weakness right hand; defect on right in double spontaneous stimulation; EEG left frontal focus	Right facial weakness; marked weakness right hand	Glioblastoma multiforme, left frontal region
H.B.	64	F	Minimal weakness right hand, arm and leg (postoperative); EEG left posterior focus	Obvious right lower facial weakness; also right arm and leg	Meningioma with malignant changes, left occipitoparietal region
L.W.	62	M	Speech disturbance; right hemihypesthesia; EEG left parietal focus	Definite right lower facial weakness; drifting right arm	Oligodendroglioma with malignant change, left posterior parietal region
H.L.	60	F	Slight drifting left arm; EEG right frontoparietal focus	Marked drifting left arm; right lower facial weakness	Meningioma, right frontoparietal region
			22nd postoperative day; no weakness in face or arm	Definite drifting right arm	Meningioma removed
M.R.	43	M	Episodes numbness left face and limbs; all neurologic findings normal; EEG right side slowing	Definite drifting left arm and leg with increased deep tendon reflexes	Pneumoencephalogram, depressed roof of right lateral ventricle, posterior portion (not operated on, diagnosis uncertain)
			Examined again 4 days later, normal findings	No weakness found	
B.B.	44	F	Suspicious drifting right arm; EEG normal to mild diencephalic dysfunction	Definite drifting right arm; right lower facial weakness	Oligodendroglioma, left frontotemporal region
M.S.	17	M	Behavior changes only; EEG right temporal spikes	Definite drifting left arm	Oligodendroglioma with meningeal involvement right temporal region
I.W.	50	M	Horizontal nystagmus in lateral gazes; left hemisensory defect; left homonymous hemianopsia; EEG right temporooccipital focus	Left lower facial weakness; drifting left arm	Glioblastoma multiforme, right posteriotemporoparietal region
M.M.	64	F	Right 8th nerve deafness; right facial weakness; slight weakness in right arm and leg; EEG diffuse bilateral bursts; diencephalic dysfunction	Same motor weakness but more marked than before	Posterior fossa metastatic lymphosarcoma
F.D.	48	F	Early choke disk, left; organic mental syndrome; EEG right frontal focus	Definite left lower facial weakness	Glioblastoma multiforme, right frontal lobe, deep
A.C.	61	M	Early papilledema; right Babinsky; speech disturbance; minimal drifting right arm and leg; EEG severe diffuse bilateral slowing, more on left with frontal accentuation	Definite right arm and leg weakness	Metastatic carcinoma left upper frontal region

TABLE 5—(Continued)

Patient	*Age*	*Sex*	*Neurologic findings before sodium Amytal test*	*Motor weakness disclosed under sodium Amytal test*	*Final diagnosis and location of lesion*
T.Mc.	58	M	Slight to moderate right hemiparesis—at times none; diffuse left side slowing, deep, in EEG	Definite drifting right arm and leg (test repeatedly done)	Glioblastoma multiforme, left upper and posterior parietal region, deep
F.A.	49	M	Convulsions, metallic taste in mouth, hemianopsia for color, left arm minimal drifting; organic mental syndrome; EEG rightside diffuse slowing	Marked drifting left arm and leg	Glioblastoma multiforme, right temporal lobe, deep
S.G.	54	F	Tremor right hand; weakness in left leg; EEG left parietal slowing	Marked drifting left arm and leg	Meningioma (recurrence 8 years), left parietal parasagittal region
A.Y.	63	M	Speech difficulty; right facial weakness; suspicious drifting right arm; EEG diffuse, left side	Marked drifting right arm; marked right facial weakness	Glioblastoma multiforme, left parietotemporal region, more temporal
S.M.	53	F	Focal seizures, right arm; EEG right superior frontal focus	Marked right leg weakness	Metastatic carcinoma, left superior parietofrontal region

numbness in the right hand associated with clumsiness. He was frequently unable to identify or name objects, and had a memory defect.

Examination revealed that his speech was clear but hesitant, and he would search for and mispronounce words. Position sense and point localization were impaired in the right hand and foot. Double simultaneous stimulation showed the phenomena of extinction and displacement in the right hand. There was no apparent motor deficit. There was no spontaneous drift of the raised and outstretched hands. However, intravenous injection of sodium Amytal revealed a definite drift of the right upper extremity. A subsequent angiogram showed a mass in the left lower parietal region. Four days later a craniotomy was performed and the tumor was subtotally removed. The patient died two days later.

Postmortem examination disclosed an infiltrating tumor in the left parietal lobe, extending to within 1 mm. of the lateral wall of the lateral ventricle. The histologic diagnosis was oligodendroglioma with moderate to marked anaplastic change.

Comment: In addition to the aphasia and sensory changes found on neurologic examination, the sodium Amytal test brought out a motor deficit in the right upper extremity. There was no weakness of the face or leg. This additional information is of confirmative value in the clinical localization of the lesion later verified at operation and at post mortem.

Case 3.—A 61 year old man was admitted to Mount Sinai Hospital on November 2, 1954, complaining of right-sided headache of one month duration and numbness in the left arm for about ten days. In October 1954 the patient was in an automobile accident, and nine days later pain appeared in the right eye associated with headache. Fourteen days after the accident numbness in the left arm developed, and four days thereafter this spread to involve the entire left upper extremity excluding the hand. On October 29, 1954 weakness in the left lower limb developed.

Examination revealed tenderness in the right frontotemporal region and slight weakness in the left leg. Double simultaneous stimulation showed the phenomena of extinction in the left-sided limbs. The intravenous injection of 0.3 gm. of sodium Amytal elicited a complete flaccid paralysis of the left arm and leg. An electroencephalogram showed diffuse bursts of slow activity over the right frontotemporoparietal region, suggesting a lesion deep in the right cerebral hemisphere. A roentgenogram of the skull revealed the pineal body to be markedly deviated to the left. On the third day of admission a right side cerebral arteriogram was done, and this revealed that the anterior aspect of the angular branch of the middle cerebral artery appeared depressed downward. The posterior portion of this vessel became dilated and extended out into the periphery. In the frontal projection the middle cerebral artery was markedly deviated over to the left side. There was a suggestion of a

TABLE 6
MOTOR WEAKNESS DISCLOSED UNDER SODIUM AMYTAL TEST IN PATIENTS OF CEREBRAL VASCULAR DISEASE

Patient	*Age*	*Sex*	*Neurologic findings before sodium Amytal test*	*Motor weakness disclosed under sodium Amytal test*	*Final diagnosis*
A.K.	40	M	Right homonymous hemianopsia; EEG left temporooccipital slowing	Weakness in right lower face, arm and leg	Lesion in left temporo-occipital region, vascular origin
E.L.	60	F	Clumsy using right fingers (3 weeks after disappearance of weakness in right arm); EEG left side diffuse	Obvious weakness in right arm and hand	Lesion in left cerebral hemisphere, vascular origin
			Same findings 14 months later; EEG normal	No weakness found	
F.A.	40	M	Left homonymous hemianopsia; EEG right posterior temporal focus	Marked right lower facial weakness	Lesion in right posterior temporal region, vascular origin
L.D.	69	M	Left 3rd cranial nerve palsy; paresis of right lateral conjugate gaze; left side ataxia; EEG normal	Weakness in left arm and leg	Lesion in midbrain, vascular origin
L.K.	52	F	Transient coma; subarachnoid hemorrhage; left arm and leg minimal weakness; EEG suppressed activity right side, diffuse	Obvious weakness left arm and leg	Craniotomy; intracerebral aneurysm; hematoma right temporal lobe; subarachnoid bleeding
G.S.	61	M	Accident, 1 month; headache, pain in O.D., numbness left leg and slight weakness; EEG diffuse right side bursts	Flaccid paralysis left arm and leg	Subdural hematoma; intracerebral hematoma, right temporal lobe (postmortem)
L.F.	41		Transient left side weakness; neurologic findings normal; EEG slight right temporal slowing	Weakness left arm, leg, and face	Occlusion, right middle cerebral artery
M.S.	65	M	Episodes of faintness and aphasia; right lower facial weakness; EEG normal	Marked aphasia; right lower facial weakness	Left cerebral vascular lesion
S.P.	47	M	Numbness both shoulders; loss of memory; EEG diffuse abnormality, left more than right	Left arm drifting	Right cerebrovascular lesion

staining related to the middle and the posterior portions of the middle cerebral artery seen in the frontal projection.

A lumbar puncture, under pressure of 230 mm. of water, revealed xanthochromic fluid. The total protein was 58 mg. per cent.

On the fourth day after admission trephinations of the skull and a right subtemporal decompression were performed, with the evacuation of clotted blood from the subdural space. Postoperatively the patient's condition fluctuated, at times he was alert and on other occasions drowsy. Two days later the wound was opened and enlarged and some thick vascular membranes and blood stained fluid were removed. Twenty hours later his respiration became stertorous. The wound was again opened and a right-sided parietotemporooccipital bone flap was turned down and some blood clots and bloody fluid were removed. After operation the patient's condition remained unchanged. As time went on his stupor deepened. Ten days later the craniotomy wound was reopened for the third time and again some clotted blood was removed. The patient showed no signs of improvement. He died four days later.

Postmortem examination disclosed a large intracerebral hematoma in the right temporal lobe involving the lower parietal area.

Comment: In this case the complete and flaccid paralysis of the left upper extremity under sodium Amytal injection suggested the presence of a lesion in the cerebrum. The postmortem examination proved that, in addition to the subdural bleeding, this patient also had a large intracerebral hematoma.

DISCUSSION

After analyzing the foregoing results, it was found that motor deficits induced by intravenous sodium Amytal were usually obtained in patients who had a lesion involving the part of the central nervous system which mediates motor function. A lesion which implicates this part of the central nervous system may not produce clinical evidence of motor weakness. Nevertheless, intravenous sodium Amytal may bring out an apparent motor weakness in the affected limb or the affected side of the face.

In 12 cases of brain tumor in which a sodium Amytal test failed to bring out any motor weakness, the pathology was craniopharyngioma, pituitary adenoma, hemangioma of the cerebellum, cerebellar astrocytoma, neurofibroma of the eighth cranial nerve, frontal pole meningioma, glioblastoma multiforme, and astrocytoma of the temporal lobe (table 4). It was shown at operation or at postmortem examination that these tumors did not directly implicate the motor pathways within the nervous system. In one patient who showed signs of a tumor involving the left occipital lobe, a motor weakness was elicited under sodium Amytal injection. However, the postmortem examination revealed a meningioma with malignant changes infiltrating the temporoparietal region from the occipital lobe, with edema extending further forward into the internal capsule and the motor cortex (H.B., table 5).

Motor deficits resulting from injury to the motor system below the cerebral level were demonstrated under sodium Amytal injection in a case of pedunculotomy for parkinsonism and in a case of a metastatic lymphosarcoma of the posterior fossa. In the former case the injury was in the pyramidal tract at the level of the brainstem and was caused by surgery, and in the latter case by neoplastic infiltration. Both cases showed a minimal weakness in the limb of the affected side, but the intravenous injection of sodium Amytal made it unquestionably obvious (table 3).

In two patients a cervicothoracic bilateral cordotomy had been done for pain. Following this operation a complete analgesia below the level of section occurred. In these cases an injection of sodium Amytal produced no motor deficit. This suggested the probability that there was no injury to the pyramidal tract. On the other hand, in two patients of cervicothoracic osteoarthropathy with long tract signs, the injection of sodium Amytal accentuated the weakness in the affected limbs. In six patients with monoplegia of the lower motor neuron order caused by poliomyelitis during their childhood, the injection of sodium Amytal did not affect the status of the motor weakness. This suggests that when there is no implication of the motor projection system, a motor deficit may not be elicited by sodium Amytal.

In the follow-up study of patients with cerebral vascular lesion, the sodium Amytal test was often positive both during the acute stage of the illness and later while the hemiparesis was disappearing. It may be persistently positive for months or years after the complete subsidence of the hemiparesis. In other instances the test was negative shortly after the recovery from the acute stage.

The electroencephalographic findings in 27 patients including 18 with brain tumor and nine with cerebrovascular lesions indicated a focal lesion in 14, diffuse abnormality in ten, and normal

record in three (one meningioma and two cerebrovascular lesions). In all these patients (tables 5 and 6) a sodium Amytal injection brought out a definite unilateral motor deficit.

In this study, although the series is not large, the results thus obtained are uniform and constant. In no instance of the control group was a motor weakness obtained under sodium Amytal injection. Also, in those patients who had shown motor weakness prior to the test, the injection of sodium Amytal either aggravated the motor weakness or did not affect its status. Whenever a minimal or suspicious motor weakness was observed, sodium Amytal would make it convincingly obvious. It brought out motor deficits which had not been suspected or previously noted. A positive sodium Amytal test indicates damage in the central nervous system. The test is simple and sensitive for motor weakness.

Sodium Amytal is a non-noxious agent. Weinstein and Kahn,[10] in their study of organic mental syndrome, injected more than 1,105 patients with sodium Amytal. There was no morbidity or mortality noted. However, they cautioned against its use in patients with severe mental deterioration or in stupor.

From the results of this study, we may suggest that sodium Amytal be used as a means to elicit latent motor deficits in the neurologic patient.

SUMMARY

1. One hundred and forty-four patients were studied for motor weakness under sodium Amytal injection, including 37 control patients. In none of these controls was a motor deficit elicited under the sodium Amytal test.

2. In the experimental group of patients with lesions involving a part of the central nervous system which mediates motor function, the injection of 150 to 500 mg. of sodium Amytal brought out motor weakness which was not elicited in the premedication examinations.

3. A minimal or suspicious motor deficit was made more conspicuous under sodium Amytal injection.

4. The sodium Amytal test is simple and sensitive for detecting motor weakness of the central origin. It is recommended as a supplementary procedure whenever its use is indicated. A positive result indicates damage to the central nervous system.

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Observations on the Effect of Thorazine on Cells In Vitro

I. General Considerations and Toxicity Assays with Slide Cultures

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EVIDENCE FOR widespread and growing interest in the use of cell cultures for studying chemical action on living systems recently was provided by a series of 27 reports published as the result of a conference on tissue culture technic in pharmacology under the sponsorship of the New York Academy of Sciences and The Tissue Culture Association.[1] The scope of the subject has been advanced notably with the introduction of methods for developing pure cell strains, long term and mass cultures, and commercial and synthetic media. As a result of such effort virologic technics have been notably enriched. While a variety of methods for drug assay have long been employed,[2] challenging new inroads have been made in the description of the action of chemical agents on cell organoids and on mitosis, as revealed in living cells with phase contrast microscopy.

In this laboratory current effort is being directed toward studying the effect of chemicals known to influence "emotional complexion" upon nervous tissue maintained in vitro. Provisional observations have been made on chlorpromazine, particularly the commercially available preparation known as Thorazine. Since our work led to inquiries on side effects producing jaundice, and because complications arose as a result of finding toxic factors in a corresponding placebo, it was thought useful to present even a fragmentary picture of work in progress, both as an illustration of methods in dynamic neurocytology and of the importance of developing new approaches in cerebral pharmacology.

The pattern of methods routinely employed in this laboratory for studying the effect of drugs on cell systems is summarized in table 1.

In spite of many drawbacks,[3] simple hanging drop preparations make available cell outgrowths which may be brought in contact with drugs, for ex-

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TABLE 1

TISSUE CULTURE METHODS USED FOR DRUG EVALUATION

Type of culture preparation	*Hanging Drop* 1. Direct observation of acute effects. 2. Evaluation of toxicity MID LID *Roller Tube* Chronic injury and death in relation to: 1. pure cell strains, or 2. societies of various cell species (e.g., brain). *Perfusion Chamber* Records of progressive acute effects to a. whole cells of various species, b. organoids of particular cells.

ample, in Columbia staining dishes, for rapid direct observations. Assays for toxicity performed by incorporating chemicals with primary explants have been described together with a list of results obtained on 110 test substances.[4]

Results are given for the minimal inhibitory dose (MID) as a point lying somewhere between the value obtained for complete inhibition of outgrowth and the concentration of the drug incorporated in the medium permitting the emigration of a few cells or, in the case of nervous tissue, of the tips of growth cones. The least injurious dose (LID) is taken as lying between the amount permitting outgrowth identical with untreated controls and the quantity in cultures showing recognizable minimal injury to the system of emigrating cells. Schneiderman[4] has pointed out that this definition of the MID and LID ". . . is a useful step away from the concept of 'critical ratio' or 'therapeutic index' as a measure of the useful potential of a drug."

While many cell types can be employed for such studies in relation to particular chemicals, interpretations must be made with due consideration of the peculiar conditions involved in testing cell systems isolated from the whole organism. However, in a study of the effect of 8-azaguanine and related compounds[5] upon human glioblastomas in vitro, the important observation was made that, in spite of certain disadvantages of working with isolated systems, ". . . it is desirable to study as fully as possible under experimental conditions the human tumors, which are the ultimate object of any chemotherapeutic program." It was also pointed out that tissue culture studies afford ". . . an important means of bridging the gap between animal tests and clinical trial," especially for the very difficult task of evaluating individual susceptibility.[5]

The roller tube method, in which two cover glasses measuring 12x50 mm. are seeded with cells on their outer faces, has been found particularly valuable in the design of a variety of experiments.[6] Thus, after culture in medium with or without test chemicals, members of the pair of cover glasses may be subjected to individual changes in the composition of the medium or may be studied under different optical conditions with a double moving picture recording instrument.

The roller tube method is well adapted for exposing cells to the effect of drugs over long periods of time to analyze the effect of chronic injury. While such observations may be made with profit on pure cell strains, special opportunities are afforded with the use of cultures containing a wide spectrum of cell types. Thus brain explants which produce complex cell societies[7] may show shifts in the behavior of members of the population, or the elimination of certain species of cells with resultant disturbances in the arrangement of the outgrowth.

Cell cultures in perfusion chambers confronted with systematic alterations in the physico-chemical environment under highly controllable conditions may be observed directly with the aid of photomicrographs or with time-lapse cinematography. The use of phase contrast microscopy for the study of entire cells, or for observations on changes in the form, position, and activity of cell organoids subsequent to the introduction of test chemicals, is proving particularly valuable when methods of film analysis are employed.[8-11]

MATERIALS AND METHODS FOR TOXICITY ASSAYS WITH SLIDE CULTURES

Explants of chick embryos were used as standard test tissues. These included 15 to 20 day spleen, five to six day heart, and nine day spinal cords, which were examined microscopically at 24 and 48 hours. Preparations with concentrations of test chemical critical to the assays were fixed and stained for further study. Experiments were run in sets of four slides for each concentration and tissue. All were repeated at least twice in the course of establishing MID and LID values. Nearly 2,000 slide cultures were employed in this study.

Thorazine (Formula J 53276), consisting of a clear solution of pure crystalline chlorpromazine hydrochloride 25 mg. per ml. of water containing ascorbic acid 2 mg., sodium bisulfite 1 mg., sodium sulfite 1 mg., and sodium chloride 6 mg., was supplied together with ampules of placebo containing the same constituents but without chlorpromazine. No difficulty was encountered in combining these solutions with culture media.

Individual constituents of Thorazine in crystalline form were also provided. Crystalline chlorpromazine hydrochloride at 2.5 per cent in distilled water produced a pH between 4 and 5. Fortunately, it was found possible to work from a 1 per cent stock solution. While this produced a milky precipitate when combined with embryonic extract, the aqueous dilutions used to cover the entire range of toxicity to cells in vitro appeared to be in true solution and did not upset the pH of the medium as compared with untreated controls. Within the range of their toxicity individual constituents of the placebo offered no special difficulties in culture preparations. It is well known that chlorpromazine decomposes on standing. Therefore, solutions of this drug and all other chemicals were freshly prepared for each test.

RESULTS

Data obtained for toxicity as revealed by incorporating test substances at various concentrations in the medium employed for the cultivation of standard chick explants in hanging drop preparations are shown in tables 2 to 6. In the first group of experiments, fluid from ampules of both Thorazine and of the corresponding placebo were incorporat-

TABLE 2

THORAZINE* (Formula J 53276)

Stock containing 25 mg./ml. of chlorpromazine hydrochloride

	MID	*LID*
Spleen	1:16 - 1:32	1:1024 - 1:2048
Heart	1:64 - 1:128	1:1024 - 1:2048
Cord	1:128 - 1:256	1:8192 - 1:16,384

PLACEBO FOR THORAZINE—(54369)*

	MID	*LID*
Spleen	> 1:4	1:32 - 1:64
Heart	1:128 - 1:256	1:1024 - 1:2048
Cord	1:4 - 1:8	1:128 - 1:256

*Furnished by Smith, Kline, and French.

ed at a constant volume of 25 per cent in the culture medium but at varying dilutions made up with Gey's balanced salt solution. Results are presented in table 2 in terms of dilutions employed, since each solution contained several different chemicals.

It will be seen that injury to explants was observed at relatively high dilutions of Thorazine, especially for the LID (least injurious dose). Heart explants, however, appeared relatively more sensitive to the placebo than to Thorazine itself. Regenerating nerve fibers from spinal cord showed slight retardation in the presence of Thorazine at a dilution of 1:8192, but emigration resembling that of untreated controls was observed at double this dilution of the drug. In keeping with previous observations on drug toxicity, outwandering of cells from spleen tissue was least affected.

Since the toxicity of a composite of several chemicals may not be predictable in terms of the sum of their individual injurious properties, it was obvious that each constituent of Thorazine should be assessed individually. The Thorazine preparation proved to be more toxic than chlorpromazine hydrochloride alone, with the exception of the LID (least injurious dose) for cord explants (see table 3 and figure 1). The concentration of the individual placebo constituents in γ/ml. (tables 4, 5 and 6) did not appear to contribute materially to an increase in the toxicity of chlorpromazine hydrochloride, when combined as Thorazine, in relation to spleen and heart explants, but did influence damage to the cord.

Since the action of chlorpromazine is of particular interest in relation to nervous tissue, a comparison of the toxicity of ascorbic acid, sodium sulfite, and so-

TABLE 3

CHLORPROMAZINE (γ/ml. of medium)

	As thorazine—25 mg./ml.		*As pure substance*	
	MID	*LID*	*MID*	*LID*
Spleen	1562 - 780	24 - 12	1250 - 625	10 - 5
Heart	390 - 195	24 - 12	312 - 156	5 - 2.5
Cord	195 - 97	3 - 1.5	78 - 39	10 - 5

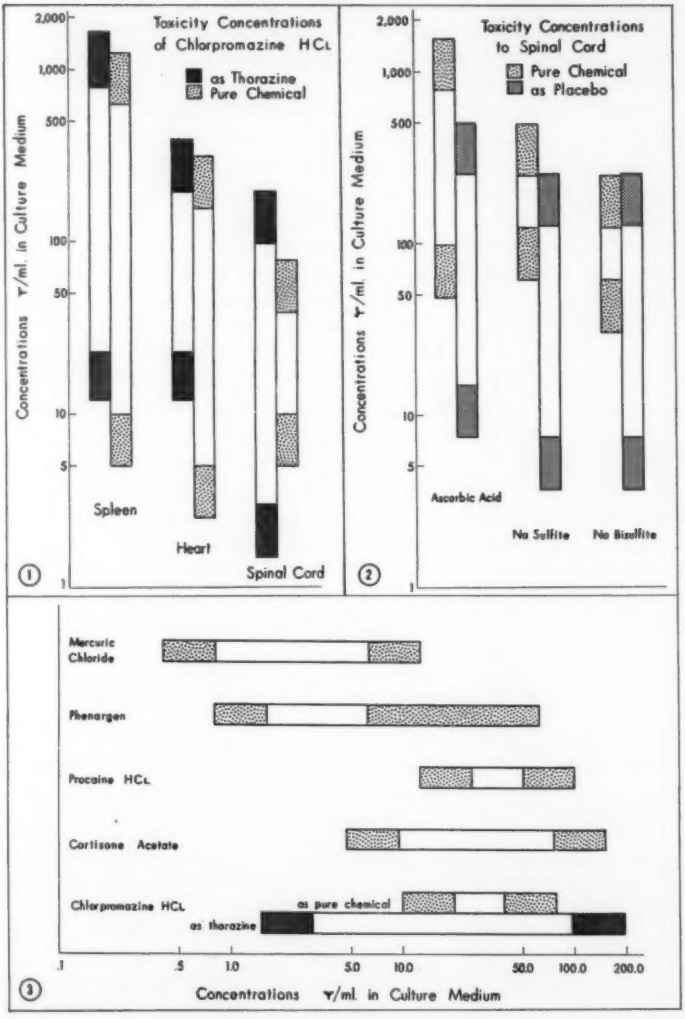

FIG. 1. Toxicity concentrations to spleen, heart, and spinal cord of chlorpromazine hydrochloride as Thorazine and as a pure chemical.

FIG. 2. Toxicity concentrations to spinal cord of pure ascorbic acid, sodium sulfite, and sodium bisulfite, and of placebos.

FIG. 3. Toxicity concentrations of several well known drugs as compared with chlorpromazine hydrochloride as Thorazine and as a pure chemical.

dium bisulfite, individually and in combination as the placebo, is shown in figure 2. Sodium chloride, which was employed at 6 mg./ml., has not been included in this analysis since previous experience with its toxic properties at the levels present in both Thorazine and the placebo would not be expected to produce injury.

The MID for ascorbic acid on cord explants is considerably greater than the value found in its relative contribution to the placebo. However, the range for the MID of sodium sulfite slightly overlaps between that for the pure substance and for the placebo. On the other hand, the effect of sodium bisulfite on the MID of the placebo is slightly greater than that which was obtained for the pure chemical. It would seem, therefore, that sodium bisulfite was the most noxious component of the mixture to nerve regeneration. While each constituent of the placebo contributed to the toxic properties of chlorpromazine, sodium sulfite and particularly sodium bisulfite were the chief offenders.

The LID for chlorpromazine as a pure substance in relation to spinal cord was somewhat less than would have been expected when used in the combination Thorazine. There remains the problem that dilutions of the placebo as a whole showed it to be somewhat more toxic to heart explants than the Thorazine solution. Perhaps in these two instances, chlorpromazine may have served to offset the toxic effects of the sulfites by depressing cellular metabolism.

For purposes of comparison, toxicity data[4] on spinal cord outgrowths are shown in figure 3 for such well known drugs as mercuric chloride, Phenergan (10-(2-Dimethylamino-1-propyl) phenothiazine), procaine hydrochloride, and cortisone acetate, in relation to the data

TABLE 4

ASCORBIC ACID (γ/ml. of medium)

	As placebo—2 mg./ml.		*As pure substance*	
	MID	*LID*	*MID*	*LID*
Spleen	> 500	62 - 31	3125 - 1562	390 - 195
Heart	15 - 7.5	1.8 - 0.9	6250 - 3125	195 - 97
Cord	500 - 250	15 - 7.5	1562 - 781	97 - 48

TABLE 5

SODIUM SULFITE (γ/ml. of medium)

	As placebo—1 mg./ml.		*As pure substance*	
	MID	*LID*	*MID*	*LID*
Spleen	> 250	31 - 15	7812 - 3906	122 - 61
Heart	7.5 - 3.7	0.9 - 0.45	3906 - 1953	244 - 122
Cord	250 - 125	7.5 - 3.7	488 - 244	122 - 61

TABLE 6

SODIUM BISULFITE (γ/ml. of medium)

	As placebo—1 mg./ml.		*As pure substance*	
	MID	*LID*	*MID*	*LID*
Spleen	> 250	31 - 15	1953 - 976	488 - 244
Heart	7.5 - 3.7	0.9 - 0.45	976 - 488	122 - 61
Cord	250 - 125	7.5 - 3.7	244 - 122	61 - 30

here reported for chlorpromazine hydrochloride. It will be noted that pure chlorpromazine hydrochloride alone has a narrower range of toxicity for the spinal cord than the others, excepting procaine hydrochloride. Indeed, the toxicity of pure chlorpromazine hydrochloride for spinal cord outgrowth is of the same order as procaine hydrochloride. On the other hand, when chlorpromazine hydrochloride is combined with redox agents as in Thorazine, its range of toxicity for nerve fiber emigration broadens.

Data of these kinds are helpful in preliminary surveys of drug action on cells in tissue culture, in directing attention to possible toxic effects at a more practical level. They provide a background for more detailed experiments on chronic injury effects with cultures in roller tubes, and in the study of cell organoids with perfusion chamber cinematographic technic employed to obtain clues regarding loci and mechanisms of action in particular cell types.

SUMMARY

1. Methods for drug assay with hanging drop slides, roller tube, and perfusion chamber cultures are reviewed.
2. With slide culture technic, the toxicity of Thorazine and a corresponding placebo of the same composition, but without the inclusion of chlorpromazine hydrochloride, have been determined.
3. Test tissues from chick embryos revealed greatest toxicity to the outgrowth from spinal cord. Heart explants were somewhat more resistant, while spleen cells were least affected.
4. The toxicity of Thorazine was greater than pure chlorpromazine hydrochloride, probably due to the presence of redox agents, particularly sodium bisulfite.
5. In comparison with data obtained from other studies on spinal cord explants, chlorpromazine hydrochloride, with a minimal dose for total inhibition of nerve outgrowth (MID) between 39 and 78 γ/ml. and the least injurious dose (LID) between 5 and 10 γ/ml. in culture medium, was of the same order as that found for procaine hydrochloride.

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Neurologic Symptoms with Osteoid Osteoma

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Osteoid osteoma was first described by Jaffe[1] in 1935. Orthopedic surgeons are well acquainted with the lesion. That it may produce signs and symptoms suggestive of a neurologic disorder has received passing comment.[2,3] The fact that this tumor may mimic certain neurologic diseases, for example, spinal cord tumor, deserves emphasis in order that an early diagnosis may be made and the patient relieved of this painful malady.

Osteoid osteoma is a benign tumor of bone. The tumor itself, often referred to as the nidus, is extraordinarily small considering the mischief it causes. Its diameter is usually only a few millimeters and rarely more than a centimeter. Histologically, the tumor resembles poorly calcified, young bone, hence the adjective "osteoid." This reddish-brown, friable mass rests in a region of densely sclerotic bone. Single lesions are the rule but multiple lesions may rarely occur. The commonest sites are the long bones, especially those of the lower extremities. The cause of the lesion is unknown.

The most striking roentgenographic change is dense sclerosis of the involved portion of the bone, often several centimeters in diameter. Near the center of this dense region may be seen a small area of radiolucency, seldom larger than 1 cm. in diameter, that is the locus of the nidus. These changes are not found with every tumor, but are common and helpful in suggesting the diagnosis when they are present.

Observations on 62 Patients

Our report is the result of a study of 62 patients who suffered from this condition. Twenty of the cases have been reviewed by Dockerty, Ghormley, and Jackson,[4] and another 13 by Purcell, Mills, and Lipscomb.[2] We included these cases in our study since interest was centered primarily on the neurologic signs and symptoms discovered in these patients.

The tumor occurs more commonly in males than in females, in a ratio of about three to one in our series (table 1). The age at which symptoms attributable to the tumor first appeared is shown in table 1. Almost no age group is immune, but in 43 of the 62 patients the first symptom appeared prior to the age of 21 years. The youngest patient was 21

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TABLE 1
OSTEOID OSTEOMA: SEX AND AGE AT ONSET OF SYMPTOMS*

Age, years	*Patients*
0 to 10	16
11 to 20	27
21 to 30	9
31 to 40	5
41 to 50	3
51 to 58	2
Total	62

*47 males and 15 females.

months and the eldest was 58 years old. Table 2 gives the location of the tumor. Approximately 80 per cent of the tumors occurred in the lower extremities.

Pain was a prominent complaint in all patients except one, a child 21 months old who was brought to the clinic because she limped. She gave no evidence of suffering from pain in the afflicted extremity. In all the other 61 patients, pain was an early, and often the first, symptom of the disease. Generally described as a "deep" ache, it was often likened to a toothache. The pain was usually steady but often became throbbing, and some patients complained of brief, sharp stabs occurring against a background of dull, steady pain. In some the pain was made worse by weight bearing, while in others it was uninfluenced by activity. The application of heat was comforting to some, while in others it increased the pain. The use of aspirin brought gratifying though temporary relief to many patients. Usually the pain was intermittent at first and in some it remained so. In others it became constant but varied unpredictably in severity. Pain at night was a prominent complaint in 51 patients. Usually they would go to bed without pain, only to be awakened after two to five hours of sleep. Some patients experienced only this night pain for months before they noted any pain during the day. As might be expected, pain was usually felt in the immediate region of the bone lesion, but in some it was experienced in regions strangely distant from the lesion. This extension or displacement of the pain could not be related to the site of the tumor. This is exemplified by three patients who had osteoid osteoma in the neck of the femur. In one the pain was felt only in the patella and down the anterior surface of the leg. In the second it seemed to begin in the groin, extending down the anterior part of the thigh and leg, and back into the lower lumbar region. In a third the pain centered in the buttock and extended down the posterior aspect of the thigh and calf.

Atrophy of some muscles of the affected extremity was noted in 33 patients. Those muscles in the immediate region of the lesion were most commonly involved, but in several cases a lesion of the shaft of the femur was attended by atrophy of the leg as well as of the thigh. In spite of definite atrophy, weakness of the atrophied muscles was rarely a complaint and was discovered on examination in only seven patients. Activity of the muscle stretch reflexes of the

TABLE 2
OSTEOID OSTEOMA: LOCATION OF LESION

Location of lesion	*Patients*
Mandible	1
Humerus	5
Scapula	2
Ulna	2
Lumbar vertebra	1
Ilium	2
Femur	30
Tibia	16
Tarsal bones	3
Total	62

involved extremity was diminished or absent in 12 patients. Usually this reduction in reflex activity occurred in atrophied muscles, but in three patients it occurred without appreciable atrophy. In two patients with lesions of the shaft of the femur, Lasègue's sign was positive. Slight but definite loss of touch and pain sensation over the lateral and anterior aspects of the thigh was found in one patient who had a tumor of the femur. Twenty-two patients limped on the affected lower extremity. In a few the limp was due to muscle weakness, in others it was attributable to pain, but in several patients no good reason for the limp could be discovered. In some of the latter group it is possible that there existed a degree of weakness sufficient to alter the gait but not great enough to be discovered by the usual method of muscle testing. Local tenderness and swelling, when present, are of value in that they direct attention to the bone lesion and obviate fruitless search elsewhere for the cause of symptoms. Table 3 depicts the frequency of these symptoms.

TABLE 3
SYMPTOMS OF OSTEOID OSTEOMA

Symptom	*Patients*
Pain	61
Night pain	51
Atrophy	33
Limp	22
Swelling	20
Tenderness	20
Diminished reflexes	12
Muscle weakness	7
Positive Lasègue's sign	2
Sensory loss	1

Relief of pain by complete surgical removal of the nidus is so common that if relief does not occur it may be assumed that the lesion was not completely removed. In eight patients previous operations in the region of the tumor produced relief of pain lasting only a few weeks to a few months. In two patients an operation was performed which was intended to remove a lesion recognized prior to operation as an osteoid osteoma. On each of these occasions the tissue removed was found to contain the nidus of an osteoid osteoma. In spite of this, relief of pain endured for only a few months. At the second operation another nidus in approximately the same region was removed, with lasting relief of pain. In one patient, "drilling" of the sclerosed bone on four occasions, done elsewhere, brought relief of pain for a few weeks each time. Complete relief of pain followed removal of the nidus. In the remaining patients, biopsy or scraping of the sclerosed bone was followed by some relief of pain, but lasting relief resulted only from identification and removal of the nidus.

Does spontaneous cure occur? The question cannot be answered with certainty. Other observers[5,6] have reported probable cases of spontaneous relief from symptoms and of disappearance of signs attributable to osteoid osteoma. One such case of possible spontaneous cure in this series has been reported elsewhere.[4] This was a seven year old girl whose symptoms disappeared slowly but completely over a three-year period without surgical treatment. Another was that of a boy who had had pain for two years at the time a diagnosis of osteoid osteoma was made on clinical grounds. The parents declined to have an operation performed. About six months after the diagnosis was made, his pain had subsided. That not all patients would escape so easily is shown by the case of a young man who came to the clinic

having suffered from pain in the right leg for two and a half years. A diagnosis of osteoid osteoma was made and surgical treatment advised. He was reluctant to accept this advice and returned home. Four and a half years later he returned, his pain unchanged. At operation an osteoid osteoma was removed and he was relieved of pain, a total of seven years after its onset.

COMMENT

In this group of 62 patients there were 14 in whom the story of pain suggested a possible neurologic disorder. The discovery of swelling, local tenderness of bone, or abnormalities of the roentgenograms resulted in a prompt diagnosis and the avoidance of unnecessary examinations. In 21 patients the character of pain plus discovery of muscle atrophy, weakness, and diminished activity of muscle stretch reflexes, singly or in combination, strongly suggested the presence of a neurologic lesion. Examination of the spinal fluid in two patients and myelographic study in three were required before a diagnosis could be made. One patient had had laminectomy and fusion of the lower part of the lumbar spinal column elsewhere in an effort to relieve him of low back and sciatic pain caused by an osteoid osteoma of the femur. The patient who had the tumor of the lumbar part of the spinal column presented a more than usually difficult problem. In this patient the tumor lacked the usual sclerotic bone about it and caused the affected pedicle to appear absent in the roentgenograms of the spinal column. It was only when the removed bone was examined by the pathologist that the diagnosis became apparent.

SUMMARY

Osteoid osteoma is a small benign tumor of bone most frequently encountered in young persons. The commonest symptom is pain. The concomitant occurrence of muscle atrophy and diminution of activity of muscle stretch reflexes in the involved extremity may erroneously suggest the presence of a primary neurologic disorder. The results of a review of 62 cases of this tumor are presented. The condition is cured by complete surgical removal of the tumor.

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Experimental Concussion

Relation of Acceleration to Physiologic Effect

B. F. Haddad, M.D., H. R. Lissner, J. E. Webster, M.D. and E. S. Gurdjian, M.D.

IN A PREVIOUS REPORT on measurements of acceleration in experimental head injury,[1] it was found that the values of acceleration varied greatly and the concussive effect was not predictable. Further studies utilizing similar technics were carried out to gain additional information concerning the relationship between acceleration and concussive effect.

METHOD

The general procedure was to anesthetize dogs of various weights with intravenous Nembutal and remove the temporalis muscles bilaterally, thus exposing the skull. The accelerometer used initially in these tests was the unbonded wire type. The range of the accelerometer was ±500 G and its natural frequency was 1,600 cycles per second. It weighed 4.3 oz. (figure 1). This accelerometer measured the duration as well as the magnitude of acceleration. In order to eliminate any error produced by the inertia of the instrument and to measure values greater than ±500 G, a barium titanate type accelerometer was used (figure 2). This instrument weighed only 0.8 oz. and could measure accelerations linearly within and beyond the limits of the experiments. However, this instrument measured only the peak acceleration and not the duration of the acceleration. In order to compare both instruments, they were secured to the same base which was then given an accelerating blow. Both instruments measured the acceleration linearly and with equal accuracy with respect to magnitude, as indicated in the graph in figure 3. The accelerometer was secured to the skull on the side opposite that which was struck. Ball peen hammers were used to deliver the blows to the head. They were padded to vary the acceleration of the head and to prevent crushing the skull.

Electrical signals from the accelerometer were amplified by Ellis amplifiers and led into a dual beam cathode ray oscilloscope. Records were made using a high speed oscilloscope camera. Blood pressure and respiration were recorded, and a concussive effect considered to be present if definite vasomotor and respiratory responses were obtained. This was characterized by a steep rise in blood pressure with respiratory arrest, usually lasting several seconds immediately after impact.

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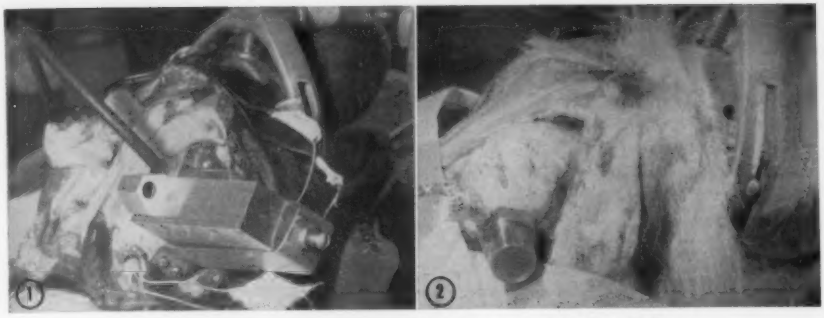

FIG. 1. The Statham accelerometer secured to the right parietal area of the dog's skull.

FIG. 2. The barium titanate accelerometer screwed into place in the right parietal area about 4 cm. from the midline.

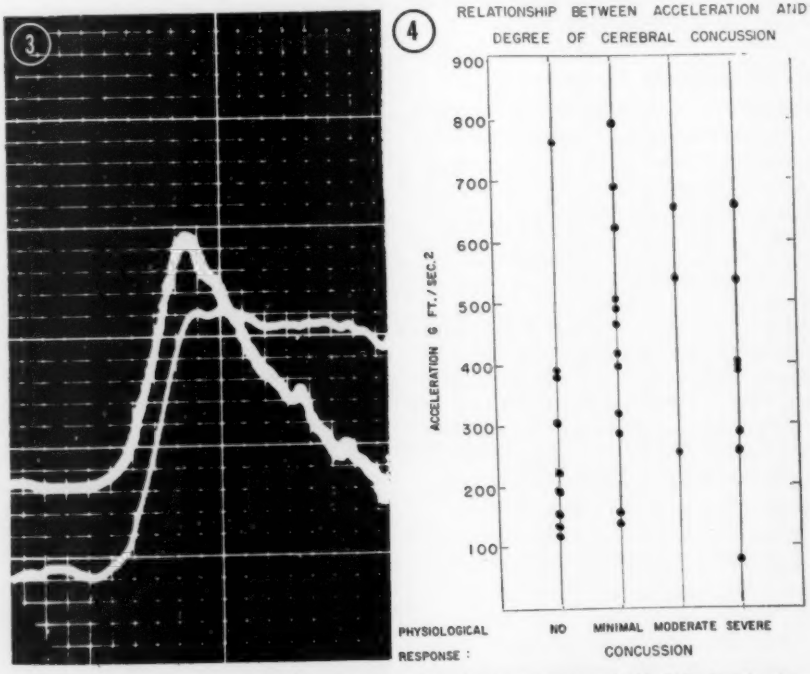

FIG. 3. The uppermost curve indicates that only peak acceleration was measured with the barium titanate accelerometer. The lower curve was obtained from the Statham accelerometer and shows that magnitude and duration of acceleration were measured.

FIG. 4. The graph shows no definite pattern between the acceleration values and the degree of concussive effect.

RESULTS

Nine animals out of the total of 34 dogs used in this series showed no concussive effect. The acceleration values in this group varied from 113 G to 750 G.

Twelve animals showed minimal concussive effects, and the acceleration values were scattered between 130 G and 780 G.

Evidences of moderate concussive effects occurred with acceleration values between 250 G and 650 G. There were three animals in this group.

In the group with severe concussive effects, the magnitude of acceleration varied from 72 G to 650 G. There were ten animals in this category.

The results are tabulated in table 1 and summarized in graph form in figure 4.

TABLE 1

ACCELERATION IN EXPERIMENTAL HEAD INJURY

Peak acceleration	*Total acceleration duration (seconds)*	*Physiologic response (degree of concussion)*
390 G	0.0005	severe
250 G	0.003	moderate
300 G		none
310 G		minimal
460 G		minimal
		severe
500 G	0.001	minimal
470 G		minimal
390 G	0.001	minimal
Est. 680 G	0.0005	minimal
380 G		none
410 G		minimal
190 G	0.0015	none
260 G	0.0005	severe
390 G	0.0015	severe
Est. 530 G	0.001	moderate
230 G	0.001	none
270 G	0.0005	severe
Est. 750 G	0.001	none
370 G	0.001	none
Est. 780 G	0.001	minimal
Est. 650 G	0.001	moderate
Est. 650 G	0.0005	severe
		severe
151 G		none
72 G		severe
150 G		minimal
113 G		none
393 G		severe
131 G		none
282 G		minimal
627 G		minimal
538 G		severe
139 G		minimal

DISCUSSION

The results indicate that there is little relationship between the magnitude of acceleration and the physiologic response evoked at the time of impact. However, as previously reported,[1] acceleration may produce physiologic effects by producing intracranial pressure gradients. It has been shown that the resultant pressures acting for certain periods of time are responsible for concussive effects obtained. It is evident that high acceleration values are necessary to produce sufficiently high intracranial pressures lasting long enough to elicit physiologic responses.

CONCLUSION

There is no constant relationship between the magnitude of acceleration and the physiologic response obtained.

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Isonicotinic Acid Hydrazide in Multiple Sclerosis

Marvin C. Korengold, M.D., Guenter R. Haase, M.D., Leonard R. Berg, M.D. and Kenneth R. Magee, M.D.

A RECENT PUBLICATION[1] has suggested that isonicotinic acid hydrazide (INH) has marked beneficial effects in patients with multiple sclerosis. The present study was designed to evaluate the therapeutic effects of this drug in a controlled series of patients with this disease.

MATERIAL

A total of 81 patients were referred with the diagnosis of multiple sclerosis. To be included in this study, it was required that the patients meet the following criteria:

1. Age at onset between 15 and 45 years.
2. History of at least two episodes.
3. Indisputable evidence of multiple lesions of the central nervous system.
4. Exclusion of other disease which may simulate multiple sclerosis.

Of 81 patients screened, 33 were accepted for the study. The remaining 48 were excluded for the following reasons:

1. Incorrect diagnosis—seventeen patients did not have multiple sclerosis, but had one of the following diseases: hereditary ataxia (five), spinal cord meningioma (one), pontine tumor (one), cervical spinal arachnoiditis (one), psychoneurosis (five), multiple cerebrovascular accidents (one), Huntington's chorea (one), and undiagnosed disease of the nervous system (two).

2. Disputed diagnosis—Fifteen patients who may have had multiple sclerosis were rejected because they failed to meet all the criteria.

3. Correct diagnosis, but excluded for other reasons—Sixteen patients were not included because of the following complicating factors: convulsive disorder, Sydenham's chorea, altered status following neurosurgical procedures, social and economic factors, and severe emotional instability.

METHOD

All patients were screened for possible pulmonary tuberculosis, hepatic, renal, or hematologic disease before initiation of isonicotinic acid hydrazide therapy. The 33 patients selected for study were paired according to age, course, and severity of disease by one of the authors who did not have direct contact with any of the patients. Arbitrarily one member of each pair was assigned to receive INH, the other member to receive an identical appearing placebo. Neither the patient, the patient's physician, nor ward

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personnel knew which patients were receiving INH or the placebo. All patients received two tablets three times daily. The total dosage of INH was 300 mg. per day. All other medications of suggested therapeutic value in this disease, including vitamins, were withheld during this study. Six patients in the INH group and eight patients in the placebo group received physical therapy. Nine patients were hospitalized for the entire three months; three received INH and six received the placebo. Two patients were hospitalized for initial studies and start of treatment. The remaining 22 patients were treated on an outpatient basis. All patients were treated for three months, with neurologic evaluation by the same observer at periodic intervals.

Changes in the neurologic status of the patients under therapy were evaluated according to two methods. The present series was assessed according to the functional scale devised by Kurtzke and Berlin:[1]

0—Normal neurologic examination.
1—Minimal signs, no symptoms or incapacity (extensor plantar response, minimal finger-to-nose ataxia, diminished vibration sense).
2—Minimal symptoms (slight weakness or stiffness, mild disturbance of gait, awkwardness, mild visuomotor disturbance).
3—Moderate symptoms (monoparesis, mild hemiparesis, moderate ataxia, disturbing sensory loss, prominent urinary or eye symptoms, or combinations of lesser dysfunctions).
4—Relatively severe symptoms not preventing ability to work or carry on normal activities of living, excluding sexual function.
5—Symptoms severe enough to preclude working, with maximal motor function permitting walking unaided up to several blocks.
6—Assistance required for walking (canes, crutches, braces).
7—Restricted to wheelchair (able to maneuver chair and enter and leave chair without aid).
8—Restricted to bed but with effective use of arms.
9—Totally helpless bed patient.
10—Death due to multiple sclerosis.

A second evaluation was based on clinical change, graded as mild, moderate, or marked.

RESULTS

One of the 33 patients discontinued treatment voluntarily after the first week because of her own complaint of "marked weakness." She would not return for evaluation. It was learned later that she had been receiving the placebo. This case is not included in the final results.

Figure 1 illustrates the results of treatment according to the scale used by Kurtzke and Berlin. Of the 16 patients who received INH, 11 did not change

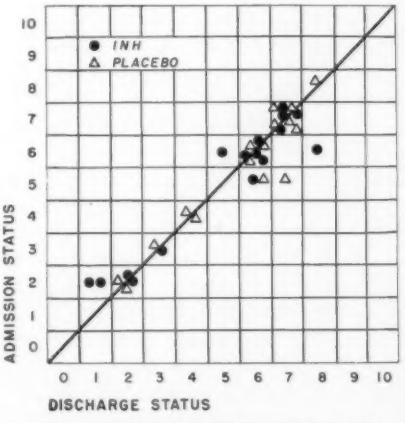

FIG. 1. This figure graphically presents the admission and discharge status of each patient. The abscissa represents the discharge status in accordance with the categories of involvement devised by Kurtzke and Berlin. The ordinate similarly represents admission status. The larger the status number, the more severe the impairment. The boxes bisected by the diagonal line represent no change in status between admission and discharge. Each dot represents a patient on isonicotinic acid hydrazide; each triangle represents a control patient.

TABLE I

FINAL CLINICAL STATUS COMPARED WITH ORIGINAL STATUS

	Better			*No Change*	*Worse*		
	Mild	*Mod.*	*Marked*		*Mild*	*Mod.*	*Marked*
INH (16 patients)	4	3	0	4	3	1	1
Placebo (16 patients)	2	1	0	9	2	1	1

their category of performance. Following treatment, two were worse by one and two categories, respectively. Three patients improved by one category each. These patients were in acute exacerbations of 17, 28, and 30 days' duration.

Of the 16 patients who received the placebo, 14 did not change their category of performance. The remaining two were worse by one and two categories, respectively. None of the control group improved sufficiently to be placed in a different functional category.

The results of clinical assessment according to estimates of mild, moderate, or marked change are given in table 1. It can be seen that by this scheme, four patients in the INH group and nine controls were unchanged. Seven of the INH patients improved, four to a mild degree and three moderately. Only three patients in the control series improved, two

TABLE 2

A SUMMARY OF PATIENT MATERIAL AND RESULTS OF TREATMENT

Patients	*Sex*	*Age*	*Age Onset*	*Duration Present Sympt.*	*Duration Illness*	*Kurtzke-Berlin Scale In*	*Out*	*General Clinical Status Unchanged*	*Improved*	*Worse*
1	F	27	19	6 mo.	96 mo.	2	2		+	
2	F	42	33	12 mo.	120 mo.	5	6			++
3	M	36	33	20 mo.	46 mo.	6	6	x		
4	F	31	19	60 mo.*	144 mo.	7	7		+	
5	M	46	22	96 mo.	300 mo.	6	6		+	
6	M	37	22	6 mo.	180 mo.	6	6		+	
7	M	47	43	1 mo.	48 mo.	6	5		++	
8	F	24	20	1 mo.	44 mo.	2	1		++	
9	F	45	18	4 mo.	60 mo.	7	7			+
10	M	40	35	18 mo.	60 mo.	6	8			+++
11	F	35	33	16 mo.*	24 mo.	7	7			+
12	M	52	40	24 mo.*	144 mo.	6	6			+
13	F	27	15	12 mo.	144 mo.	7	7	x		
14	F	44	39	14 mo.	66 mo.	2	2	x		
15	M	43	30	24 mo.	156 mo.	3	3	x		
16	F	39	23	1 mo.	192 mo.	2	1		++	
17	F	32	23	15 mo.	108 mo.	2	2		+	
18	M	39	30	24 mo.*	108 mo.	6	6			+
19	F	36	32	6 mo.	48 mo.	5	6			++
20	M	35	22	48 mo.*	156 mo.	8	8	x		
21	M	35	23	60 mo.*	144 mo.	7	7	x		
22	F	45	39	3 mo.	72 mo.	3	3	x		
23	F	50	35	48 mo.*	180 mo.	7	7	x		
24	M	37	35	4 mo.	18 mo.	4	4	x		
25	F	51	34	12 mo.	204 mo.	7	7		++	
26	M	30	26	3 mo.	48 mo.	6	6			+
27	M	41	32	12 mo.	108 mo.	7	7	x		
28	M	38	30	12 mo.	96 mo.	7	7		+	
29	F	59	39	6 mo.	240 mo.	6	6	x		
30	F	39	35	6 mo.	48 mo.	5	7			+++
31	M	38	25	24 mo.	156 mo.	4	4	x		
32	M	48	25	12 mo.	276 mo.	2	2	x		

*Progressive +Mild ++Moderate +++Marked

mildly and one moderately. Five of the INH group and four controls were worse following therapy, the degrees being approximately the same in the two groups. A summary of results of therapy is shown in table 2. No toxic reactions were noted in any patient receiving INH.

DISCUSSION

Kurtzke and Berlin reported considerably more beneficial effect from INH than was seen in the present study. In order to evaluate this discrepancy, one must consider the following differences between the two studies:

1. Their patient material was comprised almost entirely of male patients; the present group contained 16 males and 16 females divided nearly equally between INH and placebo groups.

2. Kurtzke and Berlin used as controls a series of patients treated in their hospital from 1944 to 1953. They were given various modes of therapy then popular. By contrast, the controls in the present study were evaluated simultaneously by the same personnel. They were given placebos identical in appearance with INH. The use of the double blind procedure concealed which medication a given patient received.

3. A greater proportion of the patients treated by Kurtzke and Berlin were in an exacerbation. The duration of the present episode in 15 of their 30 patients was 30 days or less. Three of their patients were treated during their first attack. By contrast, duration of the current episode in this study was 30 days or less in only three patients, and none was treated during his initial episode.

SUMMARY

1. A series of 32 patients with multiple sclerosis were given either INH or placebo preparation in a double blind procedure and observed for a period of three months. Two methods of clinical assessment were used.

2. On the Kurtzke-Berlin scale of functional improvement, 25 patients remained in the same category. No patient improved by more than one category. Three patients improved by one category. All three received INH and were initially seen during an acute exacerbation. Four patients were worse by one or two categories. Two received INH and two received the placebo.

3. The second scale of clinical assessment was based on a general estimate of the patient's status at the end of the therapy. Seven patients from the INH group and three patients from the placebo group improved. Five patients from the INH group and four patients from the placebo group were worse. Thirteen patients remained unchanged.

CONCLUSIONS

The evaluation of therapy in multiple sclerosis is difficult. Nevertheless, the following conclusions could be drawn from the present study:

1. Acute exacerbations were not prevented by the use of INH.

2. Beneficial effects of INH in multiple sclerosis were not proved.

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We are gratefully indebted to the George Washington University Multiple Sclerosis Center for assistance in obtaining patient material, to Dr. A. Dale Console of the Squibb Institute for Medical Research for supplying the placebo preparation, and to Dr. G. Milton Shy for his assistance and guidance.

Treatment of Headache with Reserpine

Arnold P. Friedman, M.D.

EACH YEAR the physician is confronted with reports of the successful results of many remedies used in the treatment of chronic headache. However, the optimistic report of the initial investigator often is not substantiated by subsequent studies. Efforts to prevent chronic headache by use of drugs have been, with few exceptions, uniformly unsuccessful. Therefore, any new drug which may be of value in the prevention of chronic headache warrants investigation.

For many years it was known in India that the plant, *Rauwolfia serpentina,* had a sedative and antihypertensive effect. Recently it has been demonstrated that reserpine, a chemically pure derivative of *Rauwolfia serpentina,* is the chief alkaloid in the plant and that it can be used safely and effectively as a tranquilizer and antihypertensive agent.[1] Since this compound is said to exert its central nervous system effect through action on the hypothalamus, which is associated so closely with the stress mechanism, it was thought advisable to study the action of this drug in patients suffering from migraine, tension, and hypertensive headaches. The purpose of this presentation is to report the results of such therapy in 220 patients during a 15 month period.

Since it is possible that the effectiveness of reserpine may vary in these specific groups of chronic headache, it is important to state clearly the diagnostic criteria used. These are:

MIGRAINE

Clinical picture: Migraine may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral, and throbbing. The headache occurs against a background of relative well-being, is often preceded by visual or psychologic disturbances, and is usually associated with vomiting and irritability.

Physiologic mechanisms: The following physiologic changes occur in an attack of migraine:[2] An initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other preheadache phenomena prior to the onset of the headache. This prodromal period is followed by dilatation and distention of cranial arteries, primarily in the distribution of the external carotid artery. Stimulation of pain-sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilatation results in a rigid, pipe-like state of the vessels. The pain at this stage is a steady ache replacing the earlier throbbing, pulsation type. During or following this, there is contraction of the neck muscles, and "muscle

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contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the headache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter, or "muscle pain," is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although in migraine the immediate cause of pain is associated with dilation of cranial arteries, it is evident that dilatation of blood vessels alone is not sufficient to produce headache. Other dynamic or chemical factors as yet not clearly delineated must contribute.

TENSION HEADACHE

Clinical picture: Tension headache occurs in relation to constant or periodic emotional conflict, of which the patients are usually partially aware. They have no prodromata, are usually bilateral, occipital, or frontal, and may be accompanied by a variety of associated signs including anxiety and nausea. Frequency and duration are variable.

Physiologic mechanisms: In tension headaches muscular or vascular mechanism may act independently or concomitantly.[3] With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia which could be a contributory or primary factor in the induction of pain. It has also been hypothecated that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory factor of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face. Under stress, a discharge may occur in the autonomic nervous system with resultant changes in the cranial blood vessels. The end organs for pain surrounding these blood vessels are stimulated and create nerve impulses which pass along the afferent pathways to the central nervous system.

HYPERTENSIVE HEADACHE

Clinical picture: The headache of arterial hypertension is usually a dull, throbbing, deep ache. It is aggravated by strain, stooping, and emotional tension. This headache may be generalized or confined to the front or back of the head. Although usually bilateral, it may resemble migraine by periodicity and being confined to one side of the head. It often appears upon awakening and may improve as the patient moves about. Nausea and vomiting are noted infrequently. Another variety of headache occurring with hypertension is suboccipital tightness and rigidity which may encircle the head.

Physiologic mechanisms: The pathogenesis of headache in essential hypertension is obscure. We do know that the degree of headache is not proportional to increased blood pressure. The headache may be present when the blood pressure is low as well as high. It is postulated that the variations in the contractile state of the cranial arteries is responsible for the headache and that the elevated blood pressure is only an accessory factor. Experimental administration of ergotamine tartrate usually abolishes the headache, which would indicate that the mechanism of pain production may be similar to migraine. This headache is not due to increased intracranial pressure since this pressure is normal, nor will elevating it experimentally produce the head pain. There is no relationship to impairment of renal function in hypertensive headache. When the blood pressure is lowered by therapeutic measures such as sodium restriction or antipressor drugs, the headache disappears.

MATERIAL AND METHODS

The 220 patients in this group were selective in that they did not respond satisfactorily to the forms of medical or psychi-

atric treatment commonly used in such patients. The symptoms were severe and tenacious. Diagnostically they were divided into the following groups: migraine—58 cases; tension headache—112 cases; hypertensive headache—50 cases.

The majority of the patients were females (160 females and 60 males). The age group ranged from 21 to 75 years, with the majority in the fourth decade. On the average the symptoms were present for five years.

Although reserpine is readily absorbed from the intestinal tract, it has a long latency of onset and slow development. Hence in headache therapy it it used essentially as a preventive or prophylactic medication and not as a form of therapy for the acute attacks of headache. The average daily maintenance dose was 0.75 mg. orally. In many cases, however, patients were effectively stabilized at 0.5 mg. There seemed to be no appreciable difference in the end results whether the drug was concentrated in the beginning of therapy or saturation was achieved slowly on a constant dose. Maximal effective action in most cases was obtained after seven to ten days of therapy. The drug was well tolerated and only mild side effects were noted. Sleepiness and dryness of the nasal mucosa, nausea, and diarrhea were noted in a small number of patients after maintenance was established. No evidence of addiction was found.

Patients with hypertension showed a reduction mainly in the systolic blood pressure, with a small reduction in the diastolic blood pressure, while the normotensive patients showed little or no blood pressure changes. The patients were observed for too short a time to evaluate the antihypertensive effect of reserpine. In general the patients described themselves as being less tense and able to overlook many usually disturbing elements in their everyday activities. A few patients reported weight gain.

RESULTS

In evaluating a drug, it is important to recognize that the efficiency of any drug does not depend upon its pharmacologic action alone.[4] The importance of dosage, timing, mode of administration, toleration by the patient, and attitude of the physician to the patient cannot be stressed sufficiently. Furthermore, such efficiency mainly depends upon the patient-physician relationship which includes, among other things, the length and frequency of interviews. Our experience indicates that the patient's reaction to drugs not only may depend upon the underlying disorder responsible for the headache, but also upon the degree of incapacity, constitutional makeup of the patient, duration of symptoms, age of individual, and psychologic status. The symbolic effect of taking a prescribed drug is also a contributory factor in treatment. All these factors must be given serious consideration in clinical usage of drugs in treatment of headache.

The patients were followed for periods ranging from three to ten months. The results are summarized in table 1. Among the 58 migraine patients, no effective results were achieved; 36 received no relief, six

TABLE 1
TREATMENT OF HEADACHE WITH RESERPINE

Type of headache	*Number of patients treated*	*Patients' response to reserpine*						*Patients' response to to placebo*
		Good		*Fair*		*Poor*		*Good*
		No.	*%*	*No.*	*%*	*No.*	*%*	*%*
Migraine	58	16	28	6	10	36	62	58
Tension	112	47	42	28	25	37	33	58
Hypertensive	50	33	66	7	14	10	20	66

reported reduced frequency of their attacks, and 16 received considerable relief. Twelve patients with migraine were placed on placebo and seven (58 per cent) responded favorably. These results with reserpine are due to the fact that in migraine sustained attitudes and emotional states provide the basis for the sequence of physiologic changes which end in headache. Therefore it is unlikely in most cases that reserpine, as now used, can produce the essential psychologic changes in the patient needed to materially alter the course of their headaches.

Among the 112 patients with tension headache, 47 showed considerable improvement in headache status, 28 showed moderate improvement, and 37 patients obtained no relief. These results must be considered in light of our favorable placebo response of 14 out of 24 (58 per cent) of tension headache patients.

Among the 50 patients with hypertensive headaches, 33 showed marked reduction in the frequency of headaches, seven reported moderate improvement, and ten showed no change in headache status. In the ten patients who obtained no relief, there was a reduction in the blood pressure similar to those who reported improvement. Although not statistically significant, four out of the six hypertensive patients given placebos showed good results (66 per cent).

The importance of placebo reaction in the clinical evaluation of a new drug cannot be overemphasized. At the present time we are utilizing the "double blind test" with patients taking reserpine. The results of this test, plus continual use of the drug, will provide a final assessment of its value in treatment of chronic headache.

The hypertensive patients had an average systolic pressure of about 180 and diastolic about 100. The highest systolic pressure was 240 and diastolic 150.

DISCUSSION

Past experience has indicated that most headaches result from an altered state of certain vascular and muscular tissues within and outside the cranium as part of the reaction of the individual to life's stresses. Chemical agents usually reduce or abolish the headache during the acute phase, but rarely control the problem for a long period. The present report is entirely too short a survey in treatment time to evaluate final results.

SUMMARY

Reserpine was given orally to 220 patients with chronic headache. Preliminary clinical evaluation in patients with hypertension showed considerable improvement, those with tension headache showed moderate improvement, and those with migraine obtained no definite relief. The present report is too short a survey time in treatment to draw final conclusions as to the effectiveness of reserpine in the treatment of chronic headache.

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CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Maurice Victor, M.D. and Lowell W. Lapham, M.D.*

PRESENTATION OF CASE

A 22 year old, white, single clerical worker was admitted to Massachusetts General Hospital for the first time because of progressive weakness of limbs and difficulty in swallowing and speaking of about two weeks' duration.

Until two years prior to admission the patient had been in good health. During the two years preceding admission, the patient complained of excessive fatigue and loss of an unknown amount of weight. She stated that she had not been obtaining sufficient sleep, and had lost her normal appetite. Her health had not been seriously impaired, however. Approximately three and one-half months prior to admission she became pregnant. Frequent vomiting developed following the onset of the pregnancy, Two months before entry, she ingested four pills of an abortifacient medication, later found to contain calcium chloride urea. Four days later the vomiting became more frequent, and she was unable to retain food.

The patient was admitted at that time to another hospital, where her symptoms improved with supportive therapy. She was discharged home, but soon had a recurrence of the vomiting. Two subsequent hospital admissions were necessary because of the vomiting, each leading to an improvement in her condition. Recurrence of vomiting took place each time she was discharged home. Three weeks prior to admission she developed lower abdominal cramps and passed an amount of vaginal blood estimated at two quarts. She was again hospitalized, and following transfusion, an abdominal hysterotomy was performed terminating the pregnancy. This was followed by improvement in the vomiting, but the patient ate poorly and her general condition remained only fair.

Approximately two weeks before admission the patient complained of rapid onset of weakness in both arms and hands, followed by steady progression. Six days before admission, the legs became weak and the patient found herself unable to walk. On the following day her voice became weak and it was difficult to swallow. She complained of paresthesias in all four extremities. Two days prior to admission the weakness had progressed to the point where the patient found herself completely unable to move her limbs. There was little change in her condition during the subsequent two days, at which time she was brought to this hospital.

During the seven days before admission the patient's urine had been dark. Five days prior to admission the patient became incontinent of urine, and this continued up until the time of admission. Intermittent abdominal cramps persisted. The past history and family history were not contributory.

Physical examination revealed a thin, emaciated, pale girl, lying immobile in bed. Her respirations were irregular and appeared difficult. Her face was expressionless. Temperature was 98.6° F., pulse 122, and respirations 34 per minute. Blood pressure was 100 mm. systolic; the diastolic pressure was not obtained. The tongue was dry, red, and coated. Examination of the abdomen disclosed no abnormal findings except for a slightly enlarged and tender liver. The heart and lungs were normal.

Examination of the nervous system revealed the patient to be mentally clear and alert. She

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attempted to cooperate as well as she was able. Cranial nerve examination demonstrated moderate facial weakness bilaterally. There was impaired swallowing and phonation, although palatal movement was fair. There was slight weakness of the sternocleidomastoid and trapezius muscles bilaterally. The remainder of the cranial nerve functions appeared to be within normal limits.

Examination of the motor system revealed a complete paralysis of all the limbs, except for feeble movements of the thumbs and fingers and some slight flexion movements of the thighs. All tendon reflexes were absent. There were no pathologic reflexes. Passive motion revealed all muscles to be flaccid. Sensory examination disclosed no abnormality to light touch, vibration, or pin prick. It was noted throughout the examination that the patient complained of severe abdominal cramps.

Laboratory examination revealed a hemoglobin of 14.3 gm. per cent. The white blood cell count was 12,000, and contained 68 per cent neutrophils, 28 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. The urinalysis revealed a specific gravity of 1.016, and a *p*H of 5.5. The test for albumin was one plus; the test for acetone two plus. The sediment contained many white blood cells in clumps. A stool guaiac test was negative. The serum calcium was 8.4 mg., and the nonprotein nitrogen was 32 mg. per cent. The total serum protein was 6.67 gm. per cent, with an albumin-globulin ratio of 1.25. The carbon dioxide combining power was 28.7 mEq., and the chloride 100 mEq. per liter. A nonprotein nitrogen on the day of death was 62 mg. per cent. A lumbar puncture performed within an hour post mortem revealed a clear cerebrospinal fluid which contained two lymphocytes, 20 mg. per cent total protein, 128 mEq. per liter chloride, and 77 mg. per cent sugar. The colloidal gold curve was normal.

On the day following admission the patient's condition was about the same. It was possible to carry out a more complete sensory examination, and no abnormalities could be detected in pain, touch, vibration, temperature, and position sense modalities. Respirations were noted to be shallow, and breathing appeared to be primarily intercostal in character. The respiratory rate at this time was 40 per minute and the pulse rate varied between 110 and 125 per minute. The blood pressure was 150/110. There was complete inability to phonate at this time and there was severe difficulty in swallowing.

On the third hospital day the respirations became more shallow, and the dyspnea became more marked, with the development of cyanosis. The patient was placed in a respirator and this was followed by improvement in her color. Nasal oxygen was administered. Gastric intubation was carried out in order to provide an adequate fluid and calorie intake. Although she had some difficulty in adjusting her respiratory rate to the rate of the respirator, her condition became stable. She frequently lapsed into sleep, but could be easily roused. No spontaneous movements were observed in any of the limbs at this time. The paralysis remained flaccid. No tenderness was noted. The sensory examination was not satisfactory on this day.

On the fourth hospital day the patient developed peripheral circulatory collapse, and expired shortly thereafter.

DIFFERENTIAL DIAGNOSIS

DR. MAURICE VICTOR: The patient under discussion presented a dramatic clinical situation. In essence, we must try to explain a neuromuscular illness of overwhelming nature, which ran its course to a lethal termination in 18 days. Of possible importance in the patient's background were the complicated pregnancy, the drug ingestion, as well as some interesting laboratory findings, but the latter features are best put aside for the moment.

Our first task is to define the nature of the disordered function, and to decide whether we are dealing with a disturbance of muscle or of peripheral nerve. Certainly these are the only logical possibilities in view of the universal involvement of the skeletal musculature, the loss of tendon reflexes, and the flaccid nature of the paralysis. On the negative side, there were no signs of long tract involvement or any other signs that would implicate the spinal cord, nor were there any specific signs of cerebral involvement.

The problem of whether we are dealing with a disease of muscle or of nerve would be readily settled if there were definite sensory signs. Unfortunately one cannot be certain of this matter. The only sensory symptoms were mild paresthesias in the extremities; all sensory modalities when tested were found to be intact. We must, therefore, employ other criteria to settle this point. The muscular disorders that could

conceivably produce the clinical picture under discussion are familial periodic paralysis, paroxysmal myohemoglobinuria, and myasthenia gravis.

The distinguishing feature of periodic paralysis is embodied in its name, that is, in the occurrence of intermittent attacks of flaccid paralysis of the trunk and limb musculature. The paralysis evolves over minutes to hours, lasts several days, spares the bulbar and respiratory muscles, and almost invariably improves. In all these respects the clinical picture differs from that of our patient. At times excessive carbohydrate ingestion precipitates an attack of periodic paralysis, during which the level of serum potassium falls. Our patient received glucose intravenously as a treatment for hyperemesis gravidarum, although no direct relation to the onset of weakness was evident. The serum potassium was not measured, but even without this information the diagnosis of periodic paralysis can be safely excluded.

Myasthenia gravis should be considered in the differential diagnosis, since it preferentially attacks young women and may begin or worsen with pregnancy. The distribution of the muscle weakness in our patient, first of the arms and hands, then of the legs and face, would be a most unusual finding in myasthenia. In the latter disease, the bulbar musculature is affected first and most severely. Despite the profound weakness of the limb and trunk musculature in our patient, there was sparing of the extraocular muscles. This also would be a most unexpected occurrence in myasthenia gravis, of which a disorder of the extraocular muscles is the commonest single manifestation.

Myohemoglobinuria, a rare disorder of muscle function, should also be considered in view of the fever, nausea, vomiting, and the history of passing of very dark urine. The onset of this condition is abrupt, much more so than was the onset in our case. The affected muscles may be weak, but this is the result of pain and swelling which are the most prominent features of the disease. The deep red color of the urine is due to myohemoglobin, and can be distinguished with certainty only by spectroscopic examination.

It would appear that myasthenia gravis, periodic paralysis, and myohemoglobinuria do not answer the clinical problem under consideration.

Let us turn to the neurologic possibilities. A fulminant illness of 18 days' duration, with successive affection of the arms, legs, and bulbar musculature, and death from respiratory paralysis, is characteristic of the syndrome referred to as Landry's paralysis. It should be clearly understood that this is an unprecise clinical term, applied to a group of symptoms and signs that may be caused by a variety of agents. If one excludes such rare causes as rabies or postinfectious encephalomyelitis, neither of which seems to pertain to our case, the diagnostic possibilities are limited. To be considered are poliomyelitis, and diphtheritic, infectious, or porphyric polyneuropathy.

Of these possibilities, diphtheritic polyneuropathy is most readily excluded. The polyneuropathy of diphtheria occurs between six and eight weeks after the original infection, and is usually preceded by pharyngeal and ciliary muscle palsies. No such sequence was evident in our patient. Furthermore, the neuropathy is usually a mixed sensory motor one and is accompanied by an elevated spinal fluid protein. Neither of these features was present in our case.

Paralytic poliomyelitis is a prime diagnostic consideration, especially since the patient was pregnant. This diagnosis could be excluded if there were a sensory deficit on examination. Unfortunately we have only the report that there were mild paresthesias in the extremities. This complaint probably meant that the sensory neurons were involved, for paresthesias could conceivably occur in the absence of actual sensory signs. Patients with palsied limbs of whatever source, however, frequently suffer tinglings of circulatory origin, and such a complaint is frequently encountered in po-

liomyelitis. The fact that so many muscles were affected and that the paralysis was so complete and symmetrical would raise doubts about the diagnosis of poliomyelitis. Such evidence, however, is not absolute. More important are the spinal fluid findings. The fluid was examined on the eighteenth day of the illness, at which time one would expect an elevation of the protein content if the patient were suffering from poliomyelitis.

The clinical features of our case are all compatible with a diagnosis of infectious polyneuritis. The tempo of the illness, the profound and symmetrical motor loss, the virtual absence of sensory signs, and the involvement of the respiratory and facial musculature are all highly characteristic. The major obstacle in accepting this diagnosis is the normal spinal fluid protein.

Finally, one must consider porphyria. Again the clinical features of the nervous system disorder are entirely in line with such a diagnosis. This is true of the spinal fluid protein as well, which may or may not be elevated in this disease. In regard to porphyria, three notations in the history are of special interest – the presence of abdominal pain, the possible drug toxicity, and the passing of dark urine. The presence of crampy abdominal pain, often severe and persistent, is highly characteristic of porphyria. The nature of this symptom is not understood and its relation to porphyria frequently passes unsuspected, so that patients with this symptom may undergo needless surgery. In our patient this symptom could easily have been overlooked, for it was overshadowed by the more dramatic symptoms of hyperemesis gravidarum. Crampy abdominal pain, however, is not a usual symptom of the latter state, and what is more significant, the pain persisted after the other toxemic symptoms had cleared.

The relation of an acute attack of porphyria to the ingestion of drugs has been frequently noted, and the term "acute toxic porphyria" has been used by some writers to designate this relationship. Almost always these drugs have been barbiturates, very occasionally lead or arsenic. There are no recorded instances of porphyria following ingestion of calcium chloride urea. The fact that the patient noted dark urine for a week prior to admission should direct our attention to porphyria, although an unqualified statement of this sort is in no way specific. The abnormal color was apparently not due to bile. If the color of the urine were dark red, it would still leave us with a number of possibilities – hematuria, hemoglobinuria, myohemoglobinuria, and porphyria. It is important to recognize that although a dark urine is usually found in symptomatic porphyria, a large variety of other illnesses are associated with porphyrinuria, that is, with the excretion of various porphyrins unrelated to the disease porphyria. Of particular diagnostic significance in porphyria is the passage of porphobilinogen in the urine. Since this evidence is lacking, however, the diagnosis must rest between infectious and porphyric polyneuropathy.

DR. L. W. LAPHAM: Before discussing the pathology, I should inform you that a test for porphobilinogen in the urine had been carried out and was positive.

DR. VICTOR: This finding simplifies matters considerably. A positive test for porphobilinogen is diagnostic of porphyria. There have been exceptions to this rule, and positive tests have been reported in cirrhosis, Hodgkin's disease, and in epileptics who are receiving anticonvulsant medication. Such instances, however, are great rarities, and the reaction under these circumstances is a very weak one, and should not cause confusion with porphyria.

A few words about testing for porphobilinogen would be helpful. The test itself is a simple one and should be part of a diagnostic work-up on all neuropathies that could conceivably be porphyric in nature. It is mandatory that a fresh urine specimen be obtained for the test. Two cc. of Watson's modified Ehrlich reagent are added to 2 cc. of urine, and to this mixture are added

4 cc. of saturated solution of sodium acetate. If a pink color appears, then 5 cc. of chloroform are added, and the mixture is shaken vigorously. If porphobilinogen is present, it will remain in the aqueous fraction. Occasionally, in the performance of this test, a pink color may be present in both the aqueous and chloroform portions. Under such circumstances, the test is unreliable and one must employ spectroscopic methods which will detect porphyrins.

PATHOLOGIC DISCUSSION

DR. LAPHAM: The general postmortem findings revealed a recent hysterotomy. There was a small amount of retained placenta. Otherwise there were no remarkable findings.

The brain, spinal cord, roots, spinal and sympathetic ganglia, and representative spinal nerves, peripheral nerves, and skeletal muscles were available for examination. No gross abnormalities were noted in any of these structures. Microscopic sections were prepared and included cell and myelin stains of the cerebral cortex, brainstem, and spinal cord; hematoxylin-eosin, fat, myelin, and axis cylinder stains of spinal and peripheral nerves; and hematoxylin-eosin stains of the skeletal muscles.

The sections of cerebral cortex demonstrated a diffuse, mild astrocytic proliferation. There were no remarkable alterations of nerve cells, and there was no significant degree of nerve cell loss. Myelin sections revealed no abnormalities of the white matter. Sections of the brainstem were normal except for a tiny recent area of infarct necrosis in the lateral medulla. There was no definite evidence of axonal reaction in the nuclei of the brainstem.

The most striking abnormalities were found in the peripheral nerves. Myelin stains of the ulnar, popliteal, posterior tibial, sciatic, and genitofemoral nerves revealed marked degeneration, consisting of swelling and globular fragmentation of myelin sheaths. This was quite pronounced in some areas and less advanced in others. In some of the sections, in addition to a segmental character of the degeneration, one could trace the changes in a few of the fibers over considerable distances, suggesting the presence of Wallerian degeneration in these fibers. The fat stains demonstrated the presence of macrophages in the degenerating areas, containing neutral fat or cholesterol esters. In many areas, however, the fragmented myelin was not yet broken down to this extent. Many large masses of disintegrating myelin, the so-called "digestion chambers," were seen in the most advanced lesions. Axis cylinder stains revealed that the process was not only one of myelin degeneration, but also severely affected axons. Numerous bulbous enlargements were seen on many of the axons, and in some areas disruption and fragmentation of axis cylinders were present. Cross sections showed that the axons had disappeared in a few of the endoneurial sheaths. Hematoxylin-eosin sections also revealed a prominence of or a relative increase in the endoneurial connective tissue. Many of the remaining Schwann cells were enlarged and there was a moderate increase in their number.

Sections containing proximal and distal portions of dorsal and ventral roots exhibited no evidence of degeneration. Spinal ganglia at several levels demonstrated no involvement of the fibers traversing the ganglia. Many of the ganglion cells were slightly swollen, their nuclei were eccentric, and the Nissl substance appeared finer than normal; this was suggestive of axonal reaction. Swollen capsular cells were sometimes seen in relation to these abnormal ganglion cells.

Sections of the spinal cord at various levels revealed swelling, chromatolysis, and eccentricity of nuclei (axonal reaction) in a small number of the anterior horn cells at several levels in the cervical, thoracic, and lumbar regions. Similar changes were observed in some of the lateral horn cells in the thoracic cord segments. A few anterior horn cells were vacuolated. There was no evidence of involvement of the white matter.

Sections of sympathetic ganglia disclosed no abnormal features.

Sartorius, gastrocnemius, triceps, and flexor digitorum longus muscles were also examined. Except for the flexor digitorum longus, which was normal, these demonstrated numerous grouped fibers smaller than 30 micra, without increase in connective tissue or evidence of inflammation. An increase in the number of sarcolemmal nuclei was present in relation to many of the small fibers. In some of the sections this degeneration was present throughout almost the entire section.

In summary, the pathologic changes indicate a severe nerve degeneration, located in the peripheral nerves predominantly, with involvement of myelin sheaths and axis cylinders, and secondary "axonal reaction" in the anterior and lateral horn cells, and possibly in the spinal ganglia. A denervation atrophy had occurred in skeletal muscles. There was no evidence of inflammatory reaction in any of the sections, and the meninges and vessels were normal.

These pathologic alterations are consistent with acute porphyria. From a strictly pathologic point of view, these changes cannot be distinguished from those of a nutritional neuropathy, although the clinical course would clearly rule out the latter condition in this case. The distribution of lesions differs from that of diphtheritic polyneuropathy as the involvement in the latter is predominantly in the spinal roots and spinal ganglia, and the degeneration is primarily in the myelin sheaths, with sparing of the axis cylinders. Infectious polyneuropathy of several days' standing usually presents an inflammatory reaction which is absent here. The same is true of the polyneuropathy associated with infectious mononucleosis. Moreover, polyarteritis nodosa is excluded by the absence of blood vessel lesions and lack of evidence of ischemic necrosis and hemorrhage in the nerves. The pathologic changes of diabetic neuropathy are not fully known, and an adequate comparison of the changes in this condition with those in the present case is not possible. This condition was ruled out clinically, however. Arsenic is capable of producing a polyneuropathy indistinguishable pathologically from that of acute porphyria, and here again the differential diagnosis depends on the clinical information. Thus, by exclusion, the diagnosis of acute porphyria with polyneuropathy is established in this case.

The striking predilection of the polyneuropathy for the motor nerves in this patient has been observed in other cases of acute porphyria, though it is not a characteristic feature. The pathologic material does not allow one to draw any conclusions with regard to this feature.

■ It is very well known that Sir Charles Bell did not give any proof of the idea that he seems to have entertained all his life, that the anterior columns of the spinal cord are the only channels by which the will exercises its power on muscles. Most of the physiologists who have experimented on this subject admit that a transverse section of the anterior columns is a cause of paralysis. Stilling alone does not admit the exactitude of this assertion. Various experiments which I will relate show how difficult it is to decide most of the questions on this subject.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Nocardiosis of the Central Nervous System

John Rankin, M.D. and Manucher Javid, M.D.

In 1888 Nocard[1] isolated an aerobic actinomycete from cattle suffering from bovine farcy. The following year Trevisan[2] named the organism *Nocardia farcinica*. The first human case of an infection due to an aerobic, acid-fast actinomycete was described by Eppinger[3] in 1890. He called the organism *Cladothrix asteroides*, but it was renamed *Nocardia asteroides* by Blanchard[4] in 1896.

Unlike *Actinomyces bovis*, *Nocardia* is found widespread in nature. An ubiquitous inhabitant of the soil, it is found on grasses and grains. It is a branching filamentous organism which is aerobic, gram-positive, and may or may not be partially acid-fast.[5,6] Most species of *Nocardia* are mere saprophytes but *Nocardia asteroides* is pathogenic in varying degree for both man and laboratory animals, gaining access to the body through the lungs.[7,8] and gastrointestinal tract or by introduction into previously traumatized tissues.[10] It may then disseminate widely by hematogenous routes. The primary lesion is most commonly found in the lungs and bronchopulmonary lymph nodes.

Notwithstanding the frequency of this organism in nature, the disease in man is rarely encountered. With few exceptions only individual cases have been reported.[8, 10–15] The pertinent features of 44 cases reported since 1890 were summarized by Cruz and Clancy[16] in 1952. Another 24 cases have been described.[5,9–11,15,17–31]

Because of the organism's propensity to spread by hematogenous routes, almost all organs have been affected. Pulmonary involvement constitutes the most common clinical manifestation, but *Nocardia* also shows a special predilection for the brain and subcutaneous tissue. In 68 cases reported to date, the lung was involved in 44 (64.7 per cent), subcutaneous tissue in 22 (32.3 per cent), and the brain in 21 (31.8 per cent). In spite of the frequency of brain involvement, the meninges were affected in only five cases. Spread of infection to serous surfaces was not uncommon, the pleura being involved in 11 instances and the peritoneum in six. In view of the frequency of metastatic brain abscesses, it is perhaps surprising that renal infection has been described in only six cases. Infection of the lymph nodes was reported on six occasions and the heart (myocardium, pericardium, and valves) on four. Gastrointestinal (three cases), osseous (three

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cases), and adrenal (two cases) involvement was infrequent. In only a single instance was the pancreas, liver, spinal cord, eye, or ear affected.

Diagnosis was established during life in only 16 of 41 fatal cases, and most of these were recognized only shortly before death. The high mortality and difficulty in diagnosis may be related, at least partly, to the frequency of brain involvement. Except for one case of meningitis,[20] all known cases of nocardiosis of the central nervous system published before 1954 were diagnosed shortly before death or at autopsy. Recently there have been three reports[28–30] of the successful treatment of nocardia brain abscess.

We feel that the necessity to record additional experiences in this previously fatal complication justifies the report of an additional successfully treated case.

CASE REPORT

A 13 year old white girl from a rural community was referred to the University Hospitals with a diagnosis of rheumatic fever on April 30, 1954. Since February 1953 she had complained of vague pains in the extremities not definitely localized to the joints. Severe attacks of left temporal and bifrontal headaches associated with sharp stabbing pain behind the left eye, blurring of vision in the right eye, and buzzing or humming in the left ear had occurred since the end of February 1954.

In the few weeks preceding her admission these symptoms were accompanied by nausea and vomiting. There had been a weight loss of 12 pounds since October 1953. A review of the past history was negative, except for an occasional slight dermatitis around the face and neck.

Physical examination revealed a bright, cooperative girl who was right-handed. Her weight was 73¾ pounds; height, 5 feet; pulse rate, 100; respiratory rate, 20; and blood pressure, 110/85 mm. Hg. Epitrochlear, cervical, and submaxillary lymph nodes were slightly enlarged. Several carious teeth were present. The liver was palpable 1 cm. and the spleen 3 cm. below the costal margins. The heart was not enlarged, and a grade I systolic murmur was heard over the pulmonary area. The lungs were clear. The only positive neurologic findings were a chronic low-grade papilledema, more marked on the left, and a complete right homonymous hemianopsia. The remainder of the physical examination was essentially negative. Before operation temperature varied between 98.6 and 100.2° F.

Peripheral blood studies on the morning following admission to the hospital showed the following: hemoglobin, 13.3 gm. per 100 cc.; red blood count, 4,370,000; and hematocrit, 40 per cent. The white blood count was 16,900, with a differential count of segmented neutrophils, 84 per cent; bands, 4 per cent; eosinophils, 1 per cent; lymphocytes, 10 per cent; and monocytes, 1 per cent. The sedimentation rate was 27 mm. in the first hour. Serology and routine agglutination studies were negative. The urine was normal. The fasting blood sugar was 91 mg. per 100 cc., and the nonprotein nitrogen 25 mg. per 100 cc. The cerebrospinal fluid was clear and colorless with a protein content of 25 mg. per 100 cc., chloride of 121 mEq. per liter, and a negative Wassermann reaction. Culture of the fluid was negative and colloidal gold curve 0000000000. An electrocardiogram was normal. An electroencephalogram showed a slow wave focus in the left parieto-occipital region. Roentgenograms of the skull and chest were reported as showing no significant abnormality. Left carotid arteriography and pneumoencephalography, however, revealed the presence of a space-occupying lesion in the left parieto-occipital region.

Operation. On May 14, 1954, immediately following pneumoencephalography, parieto-occipital osteoplastic craniotomy was performed. The dura was extremely tense, and an attempt was made to tap the left lateral ventricle, at which time an abscess was entered at a depth of 2-3 cm. from the dura. Five to 10 cc. of greenish purulent material was aspirated. After removal of a block of the cortex, a firm mass came into view. This mass was dissected away from the surrounding brain and removed in one piece with its capsule intact. Drains were left in place and the wound closed.

Pathology. The specimen, which weighed 45 gm. and measured 5.5 x 4.5 x 3.5 cm., consisted of a cerebral abscess and two small daughter abscesses (figure 1). The lesion had a thick fibrous capsule with a shaggy necrotic lining. Thick pea-green purulent material had been removed previously.

The microscopic preparation showed a necrotic fibrinopurulent exudate on the inner surface. There was some gliosis of the cerebral tissue immediately surrounding the abscess, and many inflammatory cells were present, mainly neutrophils. A single giant cell of the Langhan's type was noted in one field (figure 2).

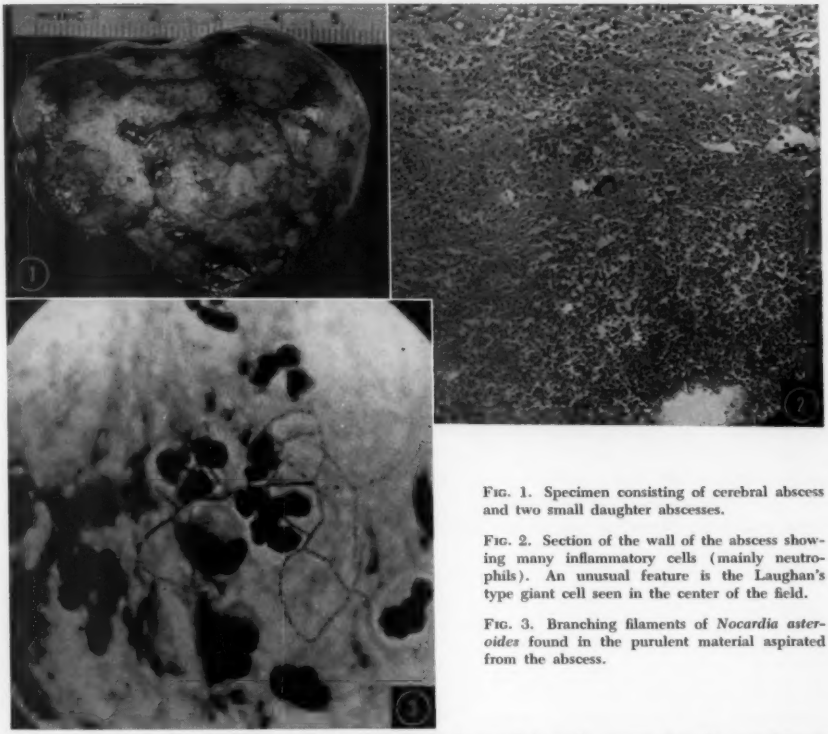

FIG. 1. Specimen consisting of cerebral abscess and two small daughter abscesses.

FIG. 2. Section of the wall of the abscess showing many inflammatory cells (mainly neutrophils). An unusual feature is the Laughan's type giant cell seen in the center of the field.

FIG. 3. Branching filaments of *Nocardia asteroides* found in the purulent material aspirated from the abscess.

Bacteriologic studies on the purulent material removed from the abscess revealed the presence of gram-positive branching filaments which on culture proved to be an aerobic actinomycete (*Nocardia asteroides*) (figure 3).

The day following surgery the white blood count rose to 23,000. The postoperative course was otherwise uneventful. The drains were gradually removed and the wound healed well.

Antimicrobial therapy. One million units of penicillin was administered intramuscularly in the operating room. This was followed postoperatively by Duracillin 300,000 units and streptomycin 0.5 gm. twice daily for seven days. At this time, a diagnosis of nocardiosis was established and treatment was continued with sulfadiazine 0.5 gm., sulfamerazine 0.5 gm., and sulfacetamide 0.5 gm. every four hours, plus Aureomycin 0.25 gm. every six hours. The sulfacetamide was discontinued after two weeks, but the other medications were continued until she was discharged from the hospital on June 8, 1954. At this time the papilledema had receded and, except for the persistence of a right homonymous hemianopsia, no neurologic deficit could be demonstrated. Treatment was continued at home on a regimen of sulfadiazine 0.3 gm. and sulfamerazine 0.3 gm. every four hours, and Aureomycin 0.25 gm. every six hours for four weeks. When seen in the neurosurgical outpatient department on July 23, 1954, she was found to have followed an excellent postoperative course. She had remained afebrile at home and had gained 17 pounds in weight. The white blood count was 5,600, hemoglobin 14.1 gm., and red blood count 4,490,000. All medications were discontinued.

The primary site of infection was never established. Numerous cultures of sputum and gastric aspirate failed to reveal *Nocardia asteroides*. Repeated roentgenograms of the chest showed no abnormality and no skin lesions were visible at any time.

She remained well and had managed very satisfactorily in school. When seen eight and

a half months after surgery on January 27, 1955, the only abnormal finding was a right homonymous hemianopsia. Careful bacteriologic examination of the sputum, peripheral blood studies, and chest x-rays showed no abnormality.

COMMENT

Review of the 23 verified cases of intracranial nocardiosis reported in literature [3, 11,13–16,20,24,28–30,32–42] reveals that there is no distinct clinical syndrome. Neurologic signs and symptoms are related only to the site and extent of the lesions within the central nervous system and to an increase in intracranial pressure. The manifestations tend to be multiple because of their metastatic origin. Purulent metastatic encephalitis is soon followed by encapsulated, frequently multilocular brain abscesses. In more chronic cases the abscess is surrounded by a nonspecific granulomatous inflammatory reaction showing neither epithelioid nor giant cells.

In the majority of recorded cases, meningeal reaction was slight or absent, while in a few frank meningitis dominated the clinical picture. A total of 23 cases of nocardiosis of the central nervous system have been reported to date. Cerebral or cerebellar abscesses were encountered in 21 cases and were complicated by meningitis on three occasions.[3,14,15] In not more than two cases[20,39] was meningitis present as the only neurologic manifestation. An additional case reported by Pribytkow and Maloletkow,[43] in which bacteriologic verification was lacking, showed meningitis and an intramedullarly cord abscess at autopsy. Postmortem examination revealed the presence of additional visceral lesions in most instances; neurologic symptoms or signs usually followed pulmonary symptoms or the finding of a subcutaneous abscess by several months. The patient described in this report is the youngest on record. Others have ranged in age from 15 to 65 years.

Even in the absence of involvement of the central nervous system, nocardiosis was invariably fatal up to 1944, but since then recovery has been reported following the use of sulfonamides alone or in combination with penicillin.[8,26,46–48] Recently improvement and recovery have been reported with Aureomycin therapy[25] and following treatment with penicillin and streptomycin.[14]

Effective medical therapy requires determination of the drug sensitivity of the organism. It must be realized, however, that the work of Runyon[44] and of Strauss and co-workers[45] has demonstrated the superiority of sulfadiazine in in vivo experiments, although other drugs such as streptomycin or Aureomycin showed similar or greater effectiveness in vitro. This would suggest that antibiotics effective in vitro should be added to rather than substituted for sulfonamides.

Where neurologic complications were present, the use of sulfonamides and antibiotics alone did not alter the prognosis except for one patient suffering from meningitis[20] who recovered following massive doses of sulfadiazine, penicillin, and Aureomycin administered by intravenous, intramuscular, and intrathecal routes.

Successful treatment appears to require surgical removal of the focus or foci along with prolonged chemotherapeutic and antibiotic therapy. This approach has been successful in three cases, in addition to the patient reported above. More than one antimicrobial agent was used in each instance, often in massive doses. In the case reported by Krueger and co-workers[28] penicillin and Aureomycin were administered postoperatively for six weeks. Following the unsuccessful use of penicillin and Aureomycin preoperatively, List and associates[29] used large doses of penicillin and sulfadiazine as well as a short course of dihydrostreptomycin for 72 days after operation. Munslow[30] successfully treated his patient with penicillin and dihydrostreptomycin for only 19 days, followed by one million units of oral penicillin daily. Sulfonamides and Aureomycin treatment probably accounted for the uneventful postoperative course in the

patient treated by us. On the other hand, antibiotic therapy in conjunction with craniotomy failed to avert the fatal outcome in four patients.[15,24,41,42]

The surgical treatment of nocardia abscesses differs little from that of other brain abscesses. Ideally the lesion should be radically excised; simple drainage is not enough because of the multilocular character of the abscess and the profuse growth of the organism. Multiplicity and dissemination of the cerebral infection no doubt accounts for many therapeutic failures, and conversely the favorable outcome in circumscribed cases when the abscess can be excised completely without rupturing its capsule.

SUMMARY

An additional case of nocardiosis of the central nervous system successfully treated is reported. A review of the literature on this subject is presented briefly.

Author's note: The patient was seen again on July 15, 1955 when the only abnormal finding was persistence of a right homonymous hemianopsia.

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■ We will now say a few words on the decussation of the conductors of tactile impressions. If a lateral half of the spinal cord has been divided transversely in the dorsal region, we find that when we touch the sole of the foot of the posterior limb on the side operated upon, the animal raises its head and tries to look at the place irritated (in which attempt it cannot succeed as its eyes are covered). On the opposite side the touching of the skin of the toes does not produce the least effect. It seems therefore that the conductors of the tactile impressions decussate in the spinal cord, as well as that of painful impressions, so that the right side of this organ transmits to the sensorium the impressions which come from the left side of the body, and vice versa. We will add that the experiments which show that the conductors of these two kinds of sensitive impressions decussate in the spinal cord are in opposition to the view that the posterior columns are the channels for both these kinds or for either of them, as it is well known that these two columns have no communication one with the other unless it be through the other parts of the cord.

C. E. Brown-Sequard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Spontaneous Carotid Thrombosis

Unusual Arteriographic Appearance

Burton L. Wise, M.D. and Jacob J. Foster, M.D.

IN RECENT YEARS, carotid thrombosis has been diagnosed with greater frequency than several decades ago, mainly because of the increased use of cerebral arteriography. The clinical picture of this condition is variable. Johnson and Walker[1] reviewed 107 cases and noted three different patterns of onset, namely, sudden catastrophic onset, slowly progressive course, and transient attacks. Fisher[2] has emphasized the frequency of carotid artery occlusion both with and without symptoms. In a series of 432 consecutive autopsies, complete unilateral or bilateral carotid occlusion was present in 28 and there was marked narrowing of the artery in 13.

The following case is reported because of the unusual appearance of the carotid angiograms, the manner of onset, and the treatment by carotid thrombectomy.

CASE REPORT

A 52 year old left-handed white male steel worker entered the hospital on July 9, 1954. While sitting quietly in a chair four days prior to admission, he suddenly complained of severe pain behind the right eye. When he attempted to walk, he dragged his left lower extremity, then fell, striking his head, but he did not lose consciousness. He was able to speak, but seemed confused.

When admitted to a county hospital that evening, he was stuporous and restless. A left spastic hemiparesis was noted, with sustained Achilles clonus and an extensor plantar response (Babinski) on the left. The pupils were round, equal, and promptly responsive to light. A spinal puncture was done shortly after admission. The fluid was clear, colorless, and contained 1 white cell per cu. mm.; the protein content was 22 mg. per cent. The pressure was not recorded.

The patient had been a professional boxer between 1920 and 1930, but had never been knocked out. There was no history of hypertension or cardiovascular or renal disease, except for occasional exertional dyspnea during the year preceding this illness. He was said to be a heavy drinker. In 1947 he was struck on the head by a falling hammer and was unconscious for several minutes.

Except for elevation of body temperature (up to 104° F.), the patient's condition remained the same for approximately 48 hours after hospitalization, when he became comatose. Upon admission to the San Francisco Veterans Administration Hospital 36 hours later, he was deeply comatose and painful stimuli caused him to assume a posture suggestive of decerebrate rigidity. Blood pressure was 150/80, pulse rate 72/min., temperature 103° F., and respirations were periodic (Cheyne-Stokes). The only significant abnormality in the general physical examination was basal pulmonary atelectasis.

The right pupil measured 3 mm. in diameter, the left 2.5 mm., and neither reacted to light. There was slight swelling of the right optic disk. A very sluggish corneal reflex was present on the right; there was no corneal reflex on the

From the neurologic surgery service of the Veterans Administration Hospital, San Francisco, and the department of neurologic surgery, University of California School of Medicine, San Francisco.

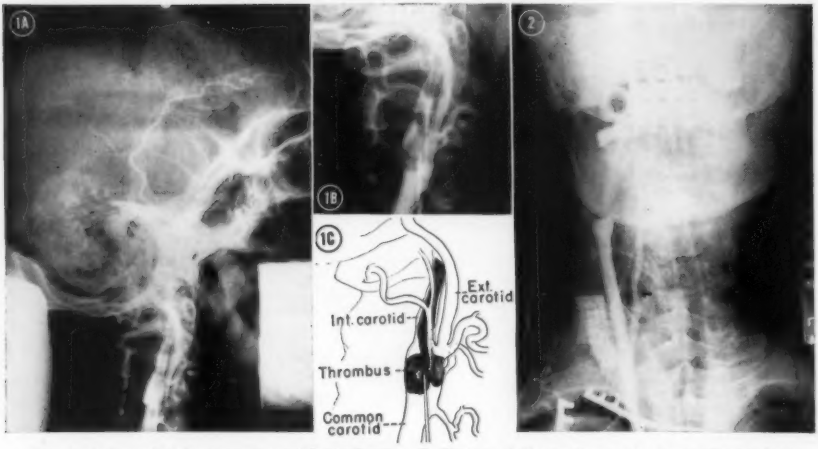

FIG. 1. *A.* Lateral right common carotid arteriogram. *B.* Portion of film in figure 1A, demonstrating shadow of thrombus outlined by Iodopyracet. *C.* Artist's drawing of same film. FIG. 2. Common carotid arteriogram. Note complete occlusion of carotid artery at its bifurcation, and retrograde filling of subclavian and vertebral arteries with Iodopyracet (arrow).

left. Bilateral hyperreflexia and extensor plantar responses were present.

A complete blood count was within normal limits. The urine contained 1 plus albumin and 3 plus sugar (following an intravenous glucose solution infusion), but was otherwise not remarkable.

Spinal fluid was clear and colorless, under a pressure of 270 mm. of water. It contained nine red cells per cu. mm., and the protein level was 36 mg. per cent (Pandy test negative). Serologic tests for syphilis were negative, and the colloidal gold curve was 1221110000.

Shortly after the patient's admission a percutaneous right carotid angiogram was done, using 35 per cent Iodopyracet. The needle entered the internal carotid artery. The injected dye filled most of the cervical portion of the internal carotid artery and extended retrograde into the common and external carotid arteries. There was a radiolucent shadow within the internal carotid which reached down to the bifurcation of the common carotid and into the initial portion of the external carotid (figure 1-A, B, C). A right common carotid angiogram was immediately done by the cut-down technic. This study demonstrated complete occlusion of the common carotid artery at its bifurcation (figure 2). After an endotracheal tube was inserted, the right common, internal, and external carotid arteries were exposed surgically, using a small amount of local anesthetic in the skin. A Potts divisional clamp was placed across the common carotid artery below the bifurcation, and a linear incision was made in the internal carotid from its origin upward for about 4 cm. A dark, firm blood clot was encountered, and the arteriotomy incision was extended downward 1 or 2 cm. into the common carotid artery. It then became apparent that the thrombus was firmly adherent to a portion of the wall of the carotid bulb, and that "tails" of thrombus extended into the internal and external carotid arteries. The thrombus was readily freed from its attachment, leaving a small, yellow, slightly irregular patch. The "tails" of the thrombus were relatively free. The portion extending up the internal carotid artery had no apparent intimal attachment and a 10 cm. length of clot was removed in one piece (figure 3) by gentle traction. However, no retrograde bleeding resulted. Several pieces of thrombus were removed from the external carotid artery, and brisk retrograde bleeding occurred. A fine polyethylene catheter was passed up the internal carotid artery for a distance of 10 cm. where it met an obstruction. Suction was applied to the catheter, but no further clot could be obtained. The arterial incision was sutured with fine silk and the incision closed in layers.

The patient never regained consciousness and expired on July 12, 1954. At autopsy thrombus was found in the entire intracranial

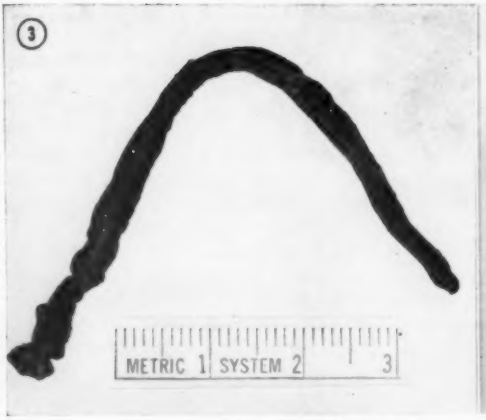

FIG. 3. Thrombus removed from internal carotid artery.
FIG. 4. Horizontal section of brain with extensive softening of right cerebral hemisphere.

portion of the right internal carotid artery, as well as the right anterior and middle cerebral arteries. There was extensive softening of the right cerebral hemisphere (figure 4).

DISCUSSION

The catastrophic onset of symptoms which took place in this patient occurs in about 35 per cent of all cases of spontaneous carotid thrombosis.[1] Headache is a common but frequently overlooked initial symptom. The sudden onset of pain behind the eye suggested a diagnosis of spontaneous subarachnoid hemorrhage to the physician who first saw this patient. Walsh and Smith[3] mentioned pain in the eye as one symptom of internal carotid artery thrombosis, but its frequency was not given. In Johnson and Walker's 107 cases,[1] headache was present in at least half of the cases, but the incidence of eye pain was not recorded.

The unusual arteriogram (figure 1) is readily explained in the light of the operative findings. The clot apparently originated at the carotid bifurcation where it was found firmly attached to about one third of the circumference of the arterial wall. The remainder of the thrombus extended distally into the internal and external carotid arteries, forming "tails" which effectively blocked blood flow through these vessels, but had not become adherent to the intima. When a needle was inserted into the internal carotid artery and Iodopyracet injected, the pressure was sufficient to force dye between the intima and the thrombus, outlining the thrombus as a relatively radiolucent zone. The fact that the dye flowed in a retrograde direction into the common and external carotid arteries, but not intracranially, indicates occlusion of the intracranial portion of the carotid artery. It is interesting to note that although the common carotid arteriogram (figure 2) demonstrated complete obstruction of the internal and external carotid arteries at their origins, the thrombus was found firmly attached to only a portion of the intimal circumference.

Thrombectomy and thromboendarterectomy have been reported infrequently in patients with carotid thrombosis. Pereira[4] attempted removal of the thrombus in three patients without improvement. Strully and co-workers[5] performed left carotid thromboendarterectomy on a 52 year old male and were able to extract a 7 cm. length of thrombus. However, they were unable to obtain a retrograde flow of blood, indicating distal carotid occlusion, and con-

sequently they ligated and excised a segment of the vessel. Recently, Eastcott and co-workers[6] reported having resected a partially occluded segment of the carotid bifurcation, followed by direct anastomosis of the common and the internal carotid arteries. This procedure apparently stopped their patient's attacks of transient left amaurosis, right hemiparesis, and aphasia.

In the patient presented here, the onset of coma which occurred 36 hours before transfer to this hospital probably was due to extension of the thrombus intracranially and into the anterior and middle cerebral arteries, with resultant extensive cerebral infarction. If thrombectomy could have been carried out earlier, intracranial extension of the thrombus might have been prevented.

If the operative findings in this case are applicable in others, it appears that a carotid thrombus may begin in and become firmly affixed to one localized area from which it then extends distally. At first the distal extension of the clot may be unattached or only loosely adherent to the intima, making removal relatively simple. Subsequently, the thrombus probably develops a firm intimal attachment, necessitating thromboendarterectomy.

It seems that thrombectomy may well be a feasible procedure shortly after carotid artery thrombosis occurs, if the thrombus originates in the common carotid or extracranial portion of the internal carotid arteries. At this time distal extensions of the clot not readily visualized might be removed by suction applied to a catheter introduced into the vessel or forced proximally by retrograde flow of blood. The risk of cerebral embolism from the carotid thrombus is probably not great if the artery is occluded proximally and the distal portion of the thrombus removed by the measures just mentioned. After the thrombus has become firmly adherent to the intima throughout its entire extent, thromboendarterectomy may be attempted, but if the thrombus reaches or extends into the cranial cavity, this procedure will probably be unsuccessful in reestablishing the continuity of the internal carotid artery.

It is becoming apparent that occlusion of the carotid arteries is a relatively common condition, which may be asymptomatic for a long period.[2] Disturbances in cerebral oxygenation, with consequent symptoms, may be precipitated by hypotension or other factors, depending on the collateral circulation.[7] The prognosis for carotid occlusion is generally poor.

Of course, reestablishment of a patent carotid lumen will not affect previous cerebral infarcts, but recurrent episodes or progression of symptoms may be prevented.

SUMMARY

A case report of a patient with spontaneous thrombosis of the right internal and external carotid arteries is presented. The unusual arteriograms, in which the dye outlined the thrombus, are reproduced. Carotid thrombectomy was accomplished without benefit to the patient. This operative procedure deserves further trial in early cases, in view of the poor results of present methods of treatment of carotid thrombosis.

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Neurology

BOOK REVIEWS

Neurochemistry, The Chemical Dynamics of Brain and Nerve

Edited by K. A. C. Elliott, Irvine H. Page, and J. H. Quastel. 1955. Springfield, Illinois: Charles C Thomas, Publisher. 900 pages. $19.50.

THIS VOLUME is as timely from the scientific standpoint as it is from the historic. As the editors point out, this volume marks the semicentennial since Thudicum produced the first work on the chemistry of the brain; thus this volume is very obviously appropriate, but its great interest and impact is in the scientific contribution. It serves as a summation and coordination of the knowledge gained in the past century in the field of the chemistry of the brain, and also opens new vistas of what might lie in the future, not only in the field of chemistry, but also in the field of neurology.

This book comprises the contributions of distinguished investigators in the field and presents, in a very orderly fashion, the current status of the field beginning with a description of the chemical constituents of the brain, the brain tissue respiration, and glycolysis on through the various metabolisms possible in the central nervous system including acetylcholine. From this vantage point the volume develops the biochemistry of the brain during early development, then turns toward defective disease by reviewing blood flow and metabolism in health and disease.

The neurologist has a vast interest in this work, not only to renew his acquaintance with the fundamental chemistry of the brain, but also to whet his appetite for a better understanding of the biochemical changes in diseases. The chapter on the biochemistry of demyelination and those on convulsive conditions are indications of the great clinical interest in this volume. The chapter on neurotrophic drugs points to potentialities for future thought and investigation, and indeed toward something better than empiricism in the matter of neurologic therapy.

This book is well illustrated with tables and diagrams of cycles of metabolism, and the bibliography is very good. There is only one unhappy note and that is the inability to keep abreast of the field. As the editors note in the introduction, the book is already somewhat out of date. This is not a criticism of the book; this is a hopeful sign for neurology, for it means that progress is being made so rapidly in this area that it is not possible to keep abreast of it.

The clinical neurologist will look with great pleasure on this new review of neurochemistry, for he has been confused for some time by the Herculean task of trying to review the biochemistry of some years

back and bring it up to date. The last preceding book on the chemistry of the brain is so hopelessly out of date now that the task was really impossible for the clinician. This volume, therefore, serves the purpose of bringing the clinicians, neurophysiologists, neuroanatomists, and neuropathologists up to date in this most important field, and serves as a stimulus for others to use the gains made by the neurochemists. Undoubtedly neurochemistry will accelerate the progress in other basic fields, such as neuropathology. This volume, but more particularly the work of its 32 collaborators, has already done much to dispel our ignorance regarding the nervous system.

F. M. F.

The Human Adrenal Cortex

Ciba Foundation Colloquia on Endocrinology. Vol. VIII. 1955. Boston: Little, Brown & Company. 665 pages. $10.00.

THIS BOOK records the papers presented at the International Conference on the Human Adrenal Cortex and, since the discussions are also included, gives the reader a feeling of presence and familiarity. The topics of 36 papers range from histologic and histochemical studies of the human adrenal cortex to more comprehensive investigations of its physiology and pharmacology. Papers of particular interest to the neurologist are "The Dynamics of Adrenal Function in Man," by P. H. Forsham and associates; "Cushing's Syndrome," one paper by L. J. Soffers and associates, and another by J. S. L. Browne and associates; "The Possible Functional Significance of the Pituitary Portal Vessels," by S. Sucherman; and "The Psychological Responses to the Administration of ACTH and Cortisone," by H. M. Fox.

No papers were presented on the subject of the innervation of the adrenal cortex nor on the central mechanism of such innervation. The volume is useful, interesting, and readable.

A. R. V.

Ageing
Volume I—General Aspects

Ciba Foundation Colloquia. 1955. Boston: Little, Brown & Company. 266 pages. $6.75.

THIS BOOK presents a series of 17 papers on the general aspects of aging. The papers are presented formally, but the conversational atmosphere is maintained in the detailed discussion which follows each essay. There is a wide variety of titles, from calcium metabolism in old age to the psychologic aspects of aging. Anatomic, histochemical, pathologic, sociologic, and nutritional studies are reported. For the jaded reader I would recommend a paper entitled "A Fantasy of Ageing and the Bearing of Nutrition on It," by R. A. McCance and E. M. Widdowson. This arresting title has nothing at all to do with any psychiatric matter. It is simply the author's way of telling his audience that he is permitting himself the privilege of high speculation about his own subject—the role of diet from the time of conception on the rate of development of senescence.

The reviewer looked carefully through the treatise and in particular at those papers which indicated a psychologic or philosophic slant, but no reference at all was found to the classic contribution on the characteristics of old age considered as a normal biologic event—Cicero's *De Senectute*. This would have been all the more appropriate since, being a dialogue, it would especially fit in a colloquy.

A. R. V.

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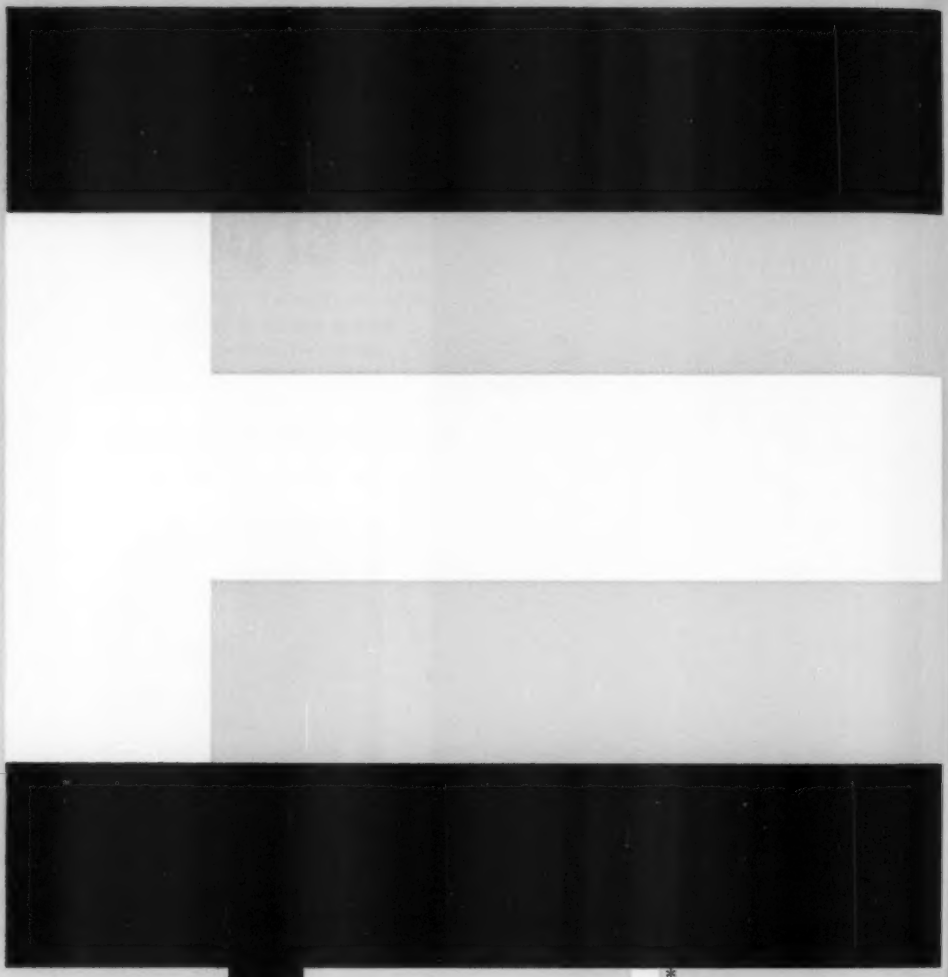

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A sterile aqueous suspension of hydrocortisone for intramuscular injection, is now being marketed by The Upjohn Company, Kalamazoo, Michigan, under the trade name Cortef Intramuscular. It is used for patients who are unable, for any reason, to take medication orally. The intramuscular injection effects are less intense and more prolonged than intravenous administration and are therefore desirable for rheumatoid arthritis patients and others who would normally get oral form. The dosage varies with the indication for use. As a temporary substitute for oral Cortef therapy, a single injection each 24 hours equivalent to daily oral dose is customarily employed and is usually sufficient. Each cc. of suspension contains 50 mg. hydrocortisone in sodium chloride with 4 mg. polysorbate 80 and 5 mg. carboxymethylcellulose.

LEDERLE AWARDS

Winners of the second annual Lederle Medical Faculty Awards have been announced. Nineteen were named. The awards are made possible by the Lederle Laboratories Division of American Cyanamid Company, Pearl River, New York, and are administered by an independent committee of professors from medical schools throughout the country. Winners are provided financial aid not in excess of $10,000 for a period of not more than three years. Application period for the 1956-57 awards has ended.

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Abbott Laboratories, North Chicago, Illinois, has announced a mild, new nonbarbiturate hypnotic, under the trade name of Placidyl, a product which offers a particularly gentle source of slumber for patients troubled by ordinary nervous insomnia. It relaxes and calms the patients. Tranquil sleep comes in 15 to 30 minutes, and should last all night. Providing mild hypnosis without the initial excitation or hangover sometimes associated with barbiturates, it is also particularly useful for those patients who awaken in the early morning.

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NOVEMBER, 1955

National Epilepsy Conference Held in France In the ancient Alsatian city of Colmar, a group of distinguished neurologists from many areas of France assembled to discuss current medical problems in epilepsy (June 18). The scientific sessions were conducted under the presidency of Professor Th. Alajouanine, and highlighted such topics as the pathophysiology of the epilepsies by Gastaut (Marseille); clinical characteristics and etiologies of infantile epilepsies by Rohmer (Strasbourg); clinical diagnosis of epilepsy in the adult by Girard (Lyon); medicosocial aspects by Castaigne (Paris); and indications for neurosurgical intervention by Woringer and Schneider (Colmar). Following spirited debates, a set of conclusions were drawn up by the conferees on the problems considered. The proceedings of the Colmar conference have been published in LES ASSISES DE MEDECINE, Vol. X, No. 4, (July) 1955.... The Colmar conference added a note of continuity in France to the colloquium on psychomotor or temporal lobe epilepsy, organized by Morin and Gastaut in Marseille (Nov. 15-18, 1954), and conducted under the auspices of the International League Against Epilepsy. According to Professors A. E. Walker and Henri Gastaut (Marseille) who are, respectively, president and president-elect of the International League Against Epilepsy, present plans call for another colloquium on temporal lobe epilepsy early in 1957, possibly in the U. S., to reappraise in the light of new experience some of the controversial points which arose in the 1955 colloquium. The conclusions to be drawn in 1957 will then be published in time for presentation and discussion at the meeting of the International League Against Epilepsy in Brussels (July 1957) during the international congresses of neurologic sciences (see Newsletter, October 1955).

M. S. Group Meets in London An impromptu conference of members of the international panel of consultants for the National Multiple Sclerosis Society was held at the National Hospital, Queen Square, London (Sept. 16). Arrangements for the meeting, which followed closely the end of the Second International Congress of Neuropathology (see Newsletter,

October 1955), were made by Drs. Douglas McAlpine (Middlesex Hospital, London) R. S. Allison (Royal Victoria Hospital, Belfast), Prof. G. H. Monrad-Krohn (Oslo), and Dr. Frederick L. Stone, director of the society's medical and scientific department. One of the purposes of the gathering was to discuss the feasibility of epidemiologic studies of multiple sclerosis on an international basis. Nineteen scientists from six countries, who attended the conference, concurred that such studies would be both feasible and conducive to additional information about the natural history of the disorder. Future discussions will be conducted through a planning committee on clinical and statistical methodology, under the auspices of the National Multiple Sclerosis Society.... Following the meeting, the conferees were entertained at supper by Sir Ernest Gowers, president of the Multiple Sclerosis Society of Great Britain and chairman of the Board of Governors, National Hospital, Queen Square.

Comments on Academy From Germany

From Prof. Dr. K. J. Zulch, Koln-Lindenthal, Germany, through Robert Wartenberg, comes this comment about the Academy and its journal, NEUROLOGY. "The struggle for an independent neurology is very obvious in America and has experienced great impetus by the foundation of the Academy of Neurology. Its postgraduate courses held every year in April are well attended. This Academy also publishes a good periodical for practitioners entitled NEUROLOGY. It might be particularly informative that this new periodical has about 3,000 subscribers, and that among these are many orthopedists, psychiatrists and workers in the other borderline fields of neurology." This excerpt (translation from the German) appeared in Deutsche Medizinische Wochenscrift, Vol. 80, No. 36, Sept. 9, 1955, p. 1313.

* * * * * *

Cerebrovascular Conference Held at NINDB

A group of neurologists and scientists assembled at the National Institute of Neurological Diseases and Blindness in Bethesda (Sept. 19) for a conference to plan a cooperative clinical study on the important problem of cerebrovascular disease. Participating in the conference were Clark H. Millikan (chairman), Raymond D. Adams, Ellen McDevitt, Miller Fisher, Albert Heyman, and Peritz Scheinberg. Representing NINDB at the conference were Gordon Seger and Seymour S. Kety. The objectives of this conference were to construct a more workable classification of vascular abnormalities of the central nervous system; to clarify the terms used by different investigators in the field in order that these terms can be employed with more precision in the future; and to devise a protocol for the collection of clin-

ical data on patients suffering cerebrovascular disease so that the data accumulated by each of the participating conferees can be compared more readily with that obtained from other investigators in different institutions. Each of the conferees and his co-workers will collect data on one or more types of cerebrovascular patients in order that eventually the natural history of different categories of cerebrovascular disease may be more accurately assessed. Results of these studies will be published jointly, if it is considered that a fruitful contribution has been made.... The conferees proposed a two-day ad hoc conference to be held in New York (December 7 and 8), at which time it is hoped that the primary problem of classification and definition will be completed, and the formulation of a protocol for the collection of data can be initiated. In the words of Chairman Clark H. Millikan of the Mayo Clinic, "It is my opinion that all members of the conference believe this an area which definitely needs cooperative investigation and intensive study. The members of the conference seem to work very well together and it is certainly my belief that we should continue the exploration of possibilities as originally outlined."

Fellowship in Pediatric Neurology Available Meyer A. Perlstein announces that a fellowship in pediatric neurology is now available at the Children's Neurology Clinic of Cook County Hospital in Chicago. The fellowship will provide clinical training in the diagnosis and rehabilitation of children with neuromuscular handicaps and participation in a clinical laboratory problem. The annual stipend varies from $3,000 to $4,000, depending upon the qualifications of the applicant. Inquiries should be forwarded to Dr. M. A. Perlstein, 4743 North Drake Avenue, Chicago 25, Ill.

Hammill Cited At Walter Reed Lt. Col. James. F. Hammill, chief of Walter Reed Army Hospital's neurology service, has been awarded a Certificate of Achievement (Sept. 19). The citation paid tribute to Col. Hammill's "many notable advances made in the training of neurology residents" and to his ability as a teacher in "combining clinical acumen and versatility to obtain the highest level of professional functioning and residency training".... Col. Hammill has begun a new assignment in the Army Surgeon General's Professional Division.

NCRND Meets in Princeton The National Committee for Research in Neurological Disorders held its third annual meeting (Sept. 28), under the chairmanship of A. B. Baker. Purpose of the meeting was to outline the program on public education on the nature of neurologic disorders as a public health problem. This committee comprises representatives from the American Academy

of Neurology and leading voluntary health agencies concerned with neurologic disabilities: National Epilepsy League, United Epilepsy Association, United Cerebral Palsy Associations, National Multiple Sclerosis Society, Muscular Dystrophy Associations, National Society for Crippled Children and Adults, National Foundation for Infantile Paralysis, and National Association for Retarded Children, (see Newsletter, July 1954). A new member attending the meeting for the first time was Dr. Grover F. Powers, representing the National Association for Retarded Children. Dr. Powers also is chairman of the Board of Trustees of the Southbury (Conn.) Training School.

Briefs The first Israel S. Wechsler lecture is to be given on the evening of December 2, 1955, at the Mount Sinai Hospital, New York City, by Dr. John F. Fulton, Sterling Professor of the History of Medicine, Yale University, School of Medicine.... The Western Institute on Epilepsy and the Western Society of Electroencephalography, of which John R. Green is general chairman, will meet at the Hotel Westward Ho, in Phoenix, Arizona (November 10-12). Guest speaker for the meeting is Wilder Penfield, and the program will include seminars on epilepsy diagnosis and treatment, clinical and research aspects of electroencephalography, and the social, educational, and employment aspects of epilepsy. This meeting is co-sponsored by the Arizona Chapter of the American Academy of General Practice and the University of Utah School of Medicine.... Percival Bailey is among the Honorary Presidents of the International Federation of Neurosurgeons (see October 1955 Newsletter).... A bust of Prof. G. H. Monrad-Krohn, who is now retired from his professorial chair, was unveiled at the Rikshospitalet, Oslo (Sept. 24)....

Percival Bailey

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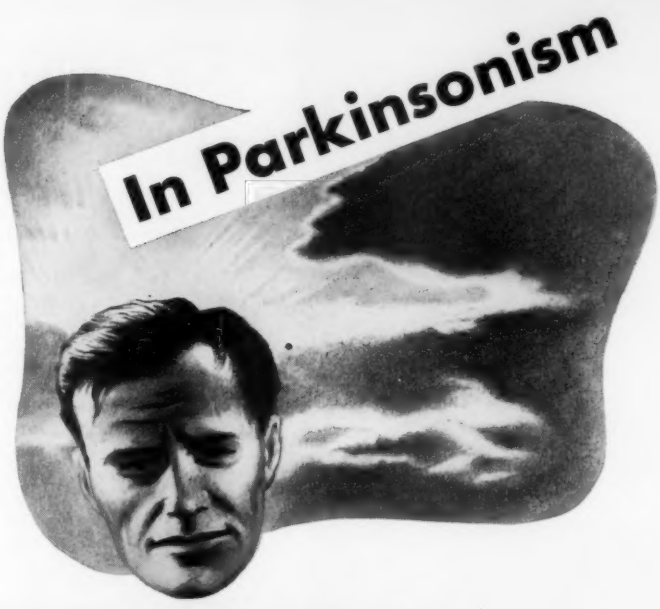

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1. Am. J. Pharm. — 117:319-326, 1945 2. N. Y. State Journal of Medicine 49/1285
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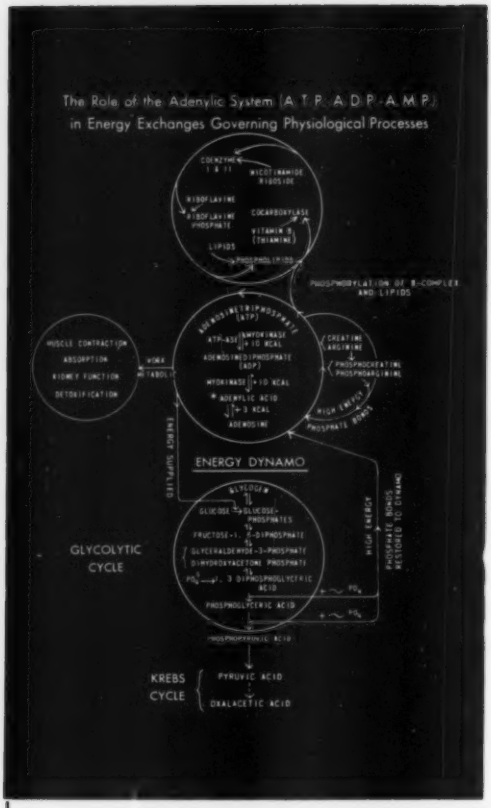

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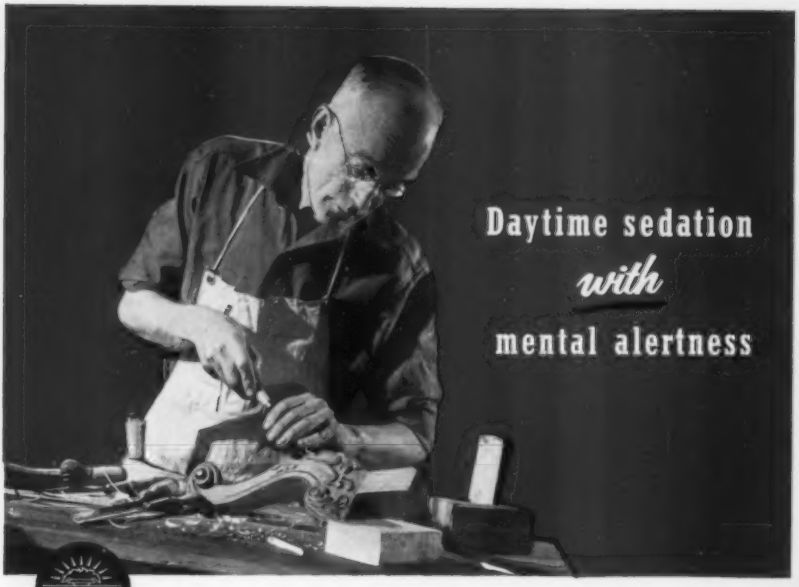

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